Commentary

USP 39–NF 34, First Supplement

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The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference between the contents of the Commentary and the official text, the official text prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the Commentary, shall prevail.

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Comments were received for the following when they were proposed in *Pharmacopeial Forum*

General Chapters:

- <17> Prescription Container Labeling
- <55> Biological Indicators–Resistance
- <191> Identification Tests—General
- <507> Protein Determination Procedures
- <791> pH
- <800> Hazardous Drugs—Handling in Healthcare Settings – *Commentary posted in separate document*
- <1050.1> Design, Evaluation, and Characterization of Viral Clearance Procedures
- <1065> Ion Chromatography
- <1207> Package Integrity Evaluation—Sterile Products
- <1207.1> Package Integrity Testing in The Product Life Cycle: Test Method Selection and Validation
- <1207.2> Package Integrity Leak Test Technologies
- <1207.3> Package Seal Quality Test Technologies
- <1228.1> Depyrogenation
- <1228.1> Dry Heat Sterilization
- <1229.5> Biological Indicators for Sterilization
- <1229.9> Physicochemical Integrators and Indicators for Sterilization
- <1229.12> New Sterilization Methods
- <2251> Adulteration of Dietary Supplements with Drugs and Drug Analogs

Monographs:

- Abacavir and Lamivudine Tablets
- Acetazolamide
- Alprazolam Extended-Release Tablets
- Amiodarone Hydrochloride Injection
- Argatroban
- Atomoxetine Capsules
- Atomoxetine Hydrochloride
- Calcium Pantothenate
- Calcium Succinate
- Candesartan Cilexetil Tablets
- Carbidopa and Levodopa Extended-Release Tablets
- Carbidopa and Levodopa Orally Disintegrating Tablets
- Cetylpyridinium Chloride
- Cyanocobalamin Tablets
- Diltiazem Hydrochloride Tablets
- Diphenhydramine Hydrochloride and Ibuprofen Capsules
- Dronedarone Hydrochloride
- Dronedarone Tablets
- Duloxetine Hydrochloride
- Fluorometholone
- Ginger
- Ginger, Powdered
- Ginger, Tincture
- Glyburide and Metformin Hydrochloride Tablets
- Goldenseal
- Goldenseal, Powdered
- Goldenseal Extract, Powdered
- Hydromorphone Hydrochloride
- Isoleucine
- Krill Oil
- Leucine
- Levothyroxine Sodium
- Lufenuron
- Orphenadarine Citrate
- Palonosetron Hydrochloride
- Perindopril Erbumine
- Perindopril Erbumine Tablets
- Rabeprazole Sodium
- *Rhodiola rosea* Capsules
- *Rhodiola rosea* Tablets
- Sildenafil Tablets
- Sodium Starch Glycolate
- Sulindac
- Sulindac Tablets
- Teniposide
- Teniposide Injection
- Triamcinolone Acetonide Nasal Spray
- Ubiquinol
- Vardenafil Hydrochloride
- Warfarin Sodium
- Zomitriptan
- Zolmitriptan Tablets

No comments received for the following when they were proposed in *Pharmacopeial Forum*

General Chapters:

- <1035> Biological Indicators for Sterilization
- <1175> Prescription Balances and Volumetric Apparatus
- <1209> Sterilization--Chemical and Physicochemical Indicators and Integrators

Monographs:

- Acetaminophen and Caffeine Tablets
- Acetazolamide for Injection
- Acetazolamide Tablets
- Adapalene Gel
- Alendronate Sodium
- Amoxapine
- Barium Hydroxide Lime
- Biological Indicator for Dry-Heat Sterilization, Paper Carrier
- Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier
- Biological Indicators for Moist Heat, Dry Heat, And Gaseous Modes Of Sterilization, Liquid Spore Suspensions
- Biological Indicator for Steam Sterilization, Paper Carrier
- Biological Indicator for Steam Sterilization, Self-Contained
- Biological Indicators for Moist Heat, Dry Heat, And Gaseous Modes Of Sterilization, Non Paper Carriers
- Bisoctrizole
- Buspirone Hydrochloride
- Buspirone Hydrochloride Tablets
- Clemastine Fumarate Tablets
- Cromolyn Sodium Ophthalmic Solution
- Dantrolene Sodium
- Dihydroxyaluminum Sodium Carbonate
- Docustae Potassium
- Edetate Disodium
- Ephedrine Hydrochloride
- Ethyl Oleate
- Etidronate Disodium
- Exemestane
- Fluorometholone Ophthalmic Suspension
- Furosemide
- Gemfibrozil Tablets
- Glutathione
- Guar Gum
- Iophendylate
- Iophendylate Injection
- Lecithin
- Levetiracetam
- Losartan Potassium Tablets
- Methylprednisolone Sodium Succinate
- Minoxidil Topical Solution
- Mesna
- Naphazoline Hydrochloride
- Oxcarbazepine Tablets
- Oxtriphylline Delayed Release Tablets
- Oxymetazoline HCl
- Paricalcitol
- Penicillin G Potassium
- Penicillin V Potassium
- Ribose
- Rimexolone Ophthalmic Suspension
- Risedronate Sodium
- Sodium Chloride and Dextrose Tablets
- Sodium Thiosulfate
- Sodium Thiosulfate Injection
- Somatropin
- Somatropin for Injection
- Succinylcholine Chloride
- Succinylchloine Chloride for Injection
- Temozolomide
- Timolol Maleate Tablets
- Triprolidine Hydrochloride
- Valproic Acid Capsules
- Ubiquinol Capsules
- Meso-Zeaxanthin
- Meso-Zeaxanthin Preparation

General Chapter/Sections: <17> Prescription Container Labeling/Multiple Sections
Expert Committee: Healthcare Quality
No. of Commenters: 3

Introduction
Comment Summary #1: The commenters suggested that an introductory paragraph be added to prevent confusion between the labeling provided by pharmaceutical manufacturers and prescription container labeling that is affixed by the pharmacy.
Response: Comments incorporated. An introductory paragraph was added that clarifies the applicability of the General Chapter to labeling instructions and information on prescription containers that are directly dispensed to the patient.

Emphasize Instructions and Other Information Important to Patients
Comment Summary #2 The commenter suggested that the following sentence be revised to be more direct by adding metric only, “The graduations on the component shall be legible and indelible, and the associated volume markings shall be in metric units and limited to a single measurement scale that corresponds with the dose instructions on the prescription container label.”
Response: Comment not incorporated. The concept of using metric units is already contained in the wording.

General Chapter/Sections: General Chapter <55> Biological Indicators-Resistance Performance Tests
Expert Committee: General Chapters—Microbiology
No. of Commenters: 5
Comment Summary #1: The commenter indicated that supplier methods vary from 1 to 5 test samples and specifically questioned the rationale for 4 test samples. In addition, the commenter suggested changing the number of BI samples to be tested to "at least 3" or "at least 4," to ensure sufficient material when testing,
Response: Comment incorporated.
Comment Summary #2: The commenters indicated that less than 100ml of water may be sufficient for blending in many cases.
Response: Comment not incorporated. The Expert Committee determined that the volume depends upon tools and techniques. An alternative volume can be used and included in the method validation.
Comment Summary #3: The commenter suggested defining the term “Chilled,” because it could be confusing to a non-US English speaker.
Response: Comment incorporated.
Comment Summary #4: The commenter indicated that if the term “agitated” was intended to be synonymous with the use of the term “blending” in the subsection for paper-fiber indicators – that consistent terminology should be used.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested using a consistent requirement for viable spore count for all types of BI’s.
Response: Comment incorporated.

Comment Summary #6: The commenter suggested that the term “labeled spore count per carrier” is not appropriate for a BI suspension and should be revised.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested that “Viable Spore Count” is more appropriate as a title for the sub-section than “Viable Cell Elimination.”
Response: Comment incorporated.
Comment Summary #8: The commenter suggested providing tolerance intervals for the heat shock times.
Response: Comment not incorporated. The Expert Committee determined that incubation to 15 min or 10 min is acceptable as it will take only a matter of seconds to remove the spore suspension and begin the next step.
Comment Summary #9: The commenter indicated that verification of rapid cooling may not be necessary before the enumeration test
Response: Comment not incorporated. The Expert Committee determined that the purpose of the ice bath was to provide the lowest possible water temperature for swiftest cooling. An alternative method of rapid cooling can be used and included in the method validation.
Comment Summary #10: The commenter questioned the need for two series of dilutions from the same original sample, if the original sample was well homogenized.
Response: Comment not incorporated. The Expert Committee determined that two series of dilutions should be used to gain a more accurate result. Duplicate plate results from each dilution are averaged as stated later in the General Chapter.
Comment Summary #11: The commenter indicated that the rationale for NLT 6 is not clear, if the recommendation is 30-300 colonies.
Response: Comment incorporated.
Comment Summary #12: The commenter indicated that the term “within” in the time prior to plating indicates timing is to be checked as this is not common in microbiological practices.
Response: Comment not incorporated. The Expert Committee determined that timing is important to ensure an accurate count without the opportunity for spore germination followed by replication. An alternative time can be used and included in the method validation.

General Chapter/Sections: <191> Identification Tests–General/Multiple Sections
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 3

General
Comment Summary #1: The commenter suggested adding examples of potential interferences within individual tests.
Response: Comment not incorporated. The Expert Committee determined that providing a non-comprehensive list of specific interferences for each test could lead to confusion. It is up to the user to ensure lack of interference.

Introduction
Comment Summary #2: The commenter suggested removing the sentence related to the usage of *Purified Water* in which “water” is mentioned without qualification, because it is redundant with the *General Notices*.
Response: Comment incorporated.

Comment Summary #3: The commenter suggested incorporating the robust statement used in the companion *Stimuli* article related to the non-exhaustive nature of the instrumental techniques described in this General Chapter, “Instrumental techniques described in this chapter may be used in lieu of chemical identification tests. Those instrumental techniques are not exhaustive and other techniques, such as nuclear magnetic resonance, ion-selective electrodes, and near-IR may be used in lieu of chemical identification test provided they are suitable and validated.”
Response: Comment incorporated.
Comment Summary #4: The commenter suggested clarifying the statement, “all chemical test procedures for the ion” and addressing the issue that an instrumental technique can display specificity for multiple ions of interest.
Response: Comment partially incorporated. The section was revised to state, “Unless otherwise specified in the monograph, if a chemical identification test is selected for an ion, then all chemical test procedures listed for the ion shall be met. If an instrumental identification test is selected, then only one instrumental technique is required for the ion(s).”

Chemical Identification Tests
Comment Summary #5: The commenter indicated that many of the chemical identification tests use a monograph style and format differing from other *USP* sections. The structure favors brevity of the descriptions rather than clear step-wise instructions resulting in difficulty in understanding the required steps of some tests for end users.
Response: Comment not incorporated. It is not possible to include extremely specific steps that help provide clarification in some cases without causing confusion for other articles. The inclusion of more details and the removal of hazardous reagents is the objective of a future revision.

Acetate
Comment Summary #6: The commenter indicated that testing steps are unclear for non-neutral solutions and that the Glacial Acetic Acid monograph directs analyst to the “lanthanum nitrate test,” but it should provide clarity on preparation wording of the testing name in relation to the *Acetate* test.
Response: Comment not incorporated. The cross-references should be clear in the monograph with the current inclusion of incises in the General Chapter.

Aluminum
Comment Summary #7: The commenter suggested adding more detail to clarify intended testing steps for end user, particularly regarding the statement, “either of these reagents”.
Response: Comment partially incorporated. The text was revised to state, “B. 1 N sodium hydroxide or sodium sulfide TS with solutions of aluminum salts produces a similar gelatinous, white precipitate, which dissolves in an excess of either of the same reagents.”

Ammonium
Expert Committee-initiated Change #1: The preparation of the indicator solution was relocated into the body of the test for clarity.

Barium
Comment Summary #8: The commenter suggested adding more detail to clarify the intended testing steps for the end user, particularly regarding the acceptance criteria by adding the terms “Criteria 1:” and “Criteria 2:”
Response: Comment not incorporated. The proposal is not consistent with the remaining chemical identification tests.

Benzoate
Comment Summary #9: The commenter suggested adding more detail to clarify intended testing steps for end user, particularly regarding the statements, “In neutral solutions” and “In moderately concentrated solutions.”
Response: Comment not incorporated. The current text is consistent with the remaining chemical identification tests. Identification tests in <191> are qualitative tests and therefore theoretically, concentration is not a critical matter. Solution preparations should be indicated in the monograph if adjustments need to be made.

Bismuth
Comment Summary #10: The commenter suggested adding more detail to clarify the intended testing steps for the end user, particularly regarding intended amounts and testing order.
Response: Comment not incorporated. The current text is consistent with the remaining chemical identification tests. Identification tests in <191> are qualitative tests and therefore theoretically concentration is not a critical matter. Solution preparations should be indicated in the monograph if adjustments need to be made.

Borate
Comment Summary #11: The commenter suggested more detail to clarify intended testing steps for end user particularly regarding a step by step approach and to update to modern laboratory pH adjustment language.
Response: Comment partially incorporated to remove the reference to litmus.

Calcium
Expert Committee-initiated Change #2: The preparation of the sample was expanded to include “or the solution prescribed in the specific monograph” for clarity.

Carbonate
Comment Summary #12: The commenter suggested separating testing and different criteria for Bicarbonate and Carbonate.
Response: Comment incorporated.
Expert Committee-initiated Change #3: The preparation of the sample was expanded to include “or the solution prescribed in the specific monograph” for clarity.

Chlorate
Comment Summary #13: The commenter suggested more detail to clarify intended testing steps for end user particularly regarding the solubility of the resulting precipitate into two separate vessels.
Response: Comment not incorporated because the current text is consistent with the remaining chemical identification tests.

Citrate
Expert Committee-initiated Change #4: The preparation of the sample was expanded to clarify that the citrate salt will be used as a solution or suspension and include “or the solution prescribed in the specific monograph” for clarity.

Cobalt
Expert Committee-initiated Change #5: The preparation of the sample was expanded to include “or the solution prescribed in the specific monograph” for clarity.

Ferric Salts
Expert Committee-initiated Change #6: A new wording “added to the ferric salts solutions” was added to compensate the separation of the original test in two tests for clarity.

Potassium
Comment Summary #14: The commenter suggested adding more detail to clarify intended testing steps for end user particularly regarding the statements: “In neutral, concentrated or moderately concentrated solutions”.
Response: Comment not incorporated because the current text is consistent with the remaining chemical identification tests. Identification tests in <191> are qualitative tests and therefore theoretically concentration is not a critical matter. Solution preparations should be indicated in the monograph if adjustments need to be made.

Salicylate
Expert Committee-initiated Change #7: A change was performed from “moderately dilute” to “moderately concentrated” sample solutions based on comments received previously.

Sodium
Comment Summary #15: The commenter suggested removing the statement “0.1 g of the sodium compound in 2 mL of water” because the individual monographs should contain the solution preparation for ease of use by end user, rather than to document a calculation to determine the 0.1 g of sodium compound at the time of each usage.
Response: Comment not incorporated because the current text is aligned with the sensitivity of this test.

Instrumental Identification Tests
Comment Summary #16: The commenters suggested removing the instrumental parameters and sample preparation in all the instrumental techniques, and to keep only the reference to the corresponding general chapter.
Response: Comment not incorporated because <191> is intended to contain the information needed for ID testing. The instrumental sections in <191> contain general information that should not conflict with the specific chapters. The referenced chapters do not contain the same amount of detail in them.
Comment Summary #17: The commenter suggested removing the concomitant analysis of standards and samples because it is in conflict with modern instrumentation using electronic libraries of spectra.

Response: Comment not incorporated because this change could lead to a new approach for USP and it requires some debate on how to apply it.
Comment Summary #18: The commenter suggested adding Near-infrared (NIR) to the techniques included in the instrumental section.
Response: Comment not incorporated because the Expert Panel concluded that the USP chapters on NIR are not ready to be added to this chapter yet. A new reference to NIR was added to the Introduction as an example of other techniques that may be used in lieu of chemical identification test provided they are suitable and validated.
Comment Summary #19: The commenter suggested removing the phrase "is the responsibility of the analyst" in the section related to the selection of the suitability of the sample preparation for the technique to be used, because the wording does not reflect practices/organizational structure in many pharmaceutical quality control laboratories.
Response: Comment incorporated.
Expert Committee-initiated Change #8: Three new sentences were added to align some changes done and for consistency: "In addition, other suitable, validated instrumental techniques may be used" and "Use USP Reference Standards where available (see Section 5.80. USP Reference Standards in the General Notices and Requirements)" and "An electronic library spectrum of the reference standard may be used for comparison to the test sample provided adequate specificity is maintained".

Identification using RAMAN Spectroscopy
Comment Summary #20: The commenters requested changing the proposed reference to chapter "Spectrophotometry and Light-Scattering <851>" to the specific chapter on RAMAN Spectroscopy.
Response: Comment incorporated. The reference was updated to "RAMAN Spectroscopy-Theory and Practice <1120>".
Comment Summary #21: The commenter suggested clarifying the instrument performance description because "verified" has a different meaning in chapter "<1226> Verification of Compendial Procedures" and it is not clear that daily checks are appropriate. It should read: "An instrument performance check and the quality of spectra collected should be evaluated at the time of use or following manufacturer's instructions."
Response: Comment incorporated.
Comment Summary #22: The commenter suggested removing the sentence "Wavelength accuracy should be verified as per applicable instrument operating procedures" because wavelength accuracy is part of instrument performance check and it is not called out in the other instrumental procedures in this chapter.
Response: Comment incorporated.
Comment Summary #23: The commenter suggested removing the sentence "All reference material and sample spectra should be collected using identical instrumental parameters" because the chapter must allow for instruments to obtain spectra of sample and standard separately, within parameters demonstrated to yield acceptable specificity.
Response: Comment not incorporated because concomitant analysis of standards and samples is the approach currently applied by USP. A policy change could lead to a new approach for USP and it requires some debate on how to apply it.
Comment Summary #24: The commenter suggested changing "collection parameters" to "instrumental parameters" for clarification.
Response: Comment incorporated.

Comment Summary #25: The commenter suggested clarifying the sample preparation of powders, solids and neat liquids because sample does not need to be transferred. Instruments may be able to obtain spectra through the primary packaging.
Response: Comment partially incorporated to "as needed" for not precluding the use of hand-held devices.
Comment Summary #26: The commenters requested changing the comparison exclusively with USP Reference Standards in the Analysis to "USP or other Qualified Reference Standard."
Response: Comment partially incorporated. The reference in this and other similar sections were changed to: "USP Reference Standards, where available" to keep the scientific principles not linked to the availability of USP Reference Standards.

Identification Using Mid-Infrared Spectroscopy
Comment Summary #27: The commenters requested aligning the record spectra described with the chapter <197>: "over the range from about 2.6 µm to 15 µm (3800 cm^{-1} to 650 cm^{-1}) unless otherwise specified in the individual monograph".
Response: Comment incorporated.

General Chapter/Sections:	<507> Protein Determination Procedures/Multiple Sections
Expert Committee:	General Chapters—Biological Analysis
No. of Commenters:	8

General Comments
Comment Summary #1: The commenters indicated their concern that their products would be required to use a procedure in General Chapter <507> once it is official.
Response: Comments not incorporated. There is no requirement to use a procedure from General Chapter <507> unless a monograph cites this General Chapters and procedure. Even if General Chapter <507> is cited, users can use their validated methods, if they give equivalent or better results than the compendial method, per *General Notices,* Section 6.30 *Alternative and Harmonized Methods and Procedure*s.
Comment Summary #2: The commenter requested that USP provide the BSA reference standard in a 1 mg/mL or 2 mg/mL configuration.
Response: Comment not incorporation. The approved USP BSA for Protein Quantitation Reference Standard (RS) is already included in this configuration.
Comment Summary #3: The commenter requested that the General Chapter be renumbered above 1000, because it seems like guidance.
Response: Comment not incorporated. General Chapter <1057> *Biotechnology-Derived Articles—Total Protein Assay* already exists for guidance purposes. General Chapter <507> contains validated procedures with system suitability criteria and a reference standard so that users can more rapidly adopt a procedure and verify that it is suitable for their particular purpose.
Comment Summary #4: The commenter stated that newer technologies now exist to measure highly concentrated proteins without dilution and suggested that these methods be added to the General Chapter.
Response: Comment not incorporated. Some new methods are sole source and not sufficiently specific for proteins (e.g. refractive index); however, in the future these methods could be added to the General Chapter, if sponsors submit their validated methods to USP.

Comment Summary #5: The commenter requested guidance on how to select an appropriate procedure.
Response: Comments not incorporated. This type of guidance belongs in above 1000 USP General Chapters and could be added to General Chapter <1057> in a future revision.
Comment Summary #6: The commenter stated that in some cases it may be better to use another reference standard rather than the USP BSA for Protein Quantitation RS for total protein quantitation.
Response: Comment not incorporated. The General Chapter already states that ideally a specific USP RS should be used and that the USP BSA for Protein Quantitation Reference Standard (RS) is for use in those cases in which another RS does not exist (note also that this RS is only listed in the colorimetric procedures II-IV). In addition, until a monograph cites the <507> procedure, users can choose and validate their own procedure and RS.

Procedure, Methods 1A and 1B
Comment Summary #7: Two commenters stated that the text regarding selection of the particular absorbance method should be edited, because verification of the choice should be sufficient.
Response: Comments incorporated. The text was changed as shown, "…and users should select which is the more suitable method based on their protein and verify, as appropriate ~~must verify which is more suitable for their particular protein sample~~."
Comment Summary #8: The commenter suggested removing the "s"s after tyrosine and tryptophan.
Response: Comment not incorporated. The Expert Committee determined that the text as written is suitable.
Comment Summary #9: The commenters stated that Sample buffers A and B may not be suitable for all proteins and suggested revisions to allow for other buffers or not diluting at all.
Response: Comments not incorporated. The methods shown were validated for several different proteins, but users must verify that the method is suitable for their particular application. As described in the response to Comment Summary #1, alternative procedures are allowed per *General Notices* 6.30.
Comment Summary #10: The commenter requested a revision to the *Reference solution* specifications in *Method 1A*.
Response: Comment incorporated. Text was modified to state, "Prepare 6 M guanidine hydrochloride in Sample buffer A ~~and 20 mM sodium phosphate, pH 6.5~~ by mixing…"
Comment Summary #11: The commenters suggested using alternative wavelengths such as 320 and 340 or preparing a plot along a range from 320 to 350 nm to correct for light scattering, rather than just the 330 nm wavelength.
Response: Comments not incorporated. The methods were validated as written. The Expert Committee will consider future revisions to the General Chapter, upon the receipt of the necessary supporting data. In addition, alternative procedures are allowed per *General Notices* 6.30 as discussed in Comment Summary #1.
Comment Summary #12: The commenter requested revisions to the equations that to help clarify the units, etc.
Response: Comment not incorporated. The Expert Committee determined that the equations were suitably worded.
Comment Summary #13: The commenters suggested modifying the *Sample preparation A* and *System Suitability* sections to align the measured absorbance requirements and the protein

concentrations. In addition, they suggested that the 0.4-0.6 absorbance requirement was too narrow and should allow any value within the linear range.
Response: Comments partially incorporated. The *Sample preparation A* text in both *Methods 1A* and *1B* were revised as shown, "Dilute the test sample by adding Sample buffer A to achieve ~~a final concentration of about 0.4 mg/mL of protein achieving~~ an absorbance of about 0.4 to 0.6". The system suitability absorbance requirement was not broadened, because linearity on some instruments can vary and the validation of this method found this range most suitable.
Comment Summary #14: The commenters suggested that duplicates were sufficient for these more precise UV methods.
Response: Comment not incorporated. The methods were validated as written. The Expert Committee will consider future revisions to the General Chapter, upon the receipt of the necessary supporting data.
Comment Summary #15: The commenter requested that the General Chapter include a reference to information on amino acid extinction coefficients.
Response: Comment not incorporated. The method was validated, using the General Chapter equations as shown, and it is not USP practice to include literature references in General Chapters numbered below 1000.
Comment Summary #16: The commenter requested deletion of the system suitability requirement for the maximum and minimum absorbance criteria.
Response: Comment not incorporated. This system suitability criterion demonstrates the specificity of the method and is suitable.

Method II–Method IV
Comment Summary #17: The commenter suggested that these methods should be removed, because they are more suitable for research and development laboratories and that a statement be added that they are not normally used for quality control laboratories.
Response: Comment not incorporated. The methods are in use in quality control laboratories for certain purposes and it is up to the user to select a method and demonstrate suitability for a particular purpose.

Method II. Bicinchoninic Acid Method
Comment Summary #18: The commenter stated that footnote 1 should be added to the Copper sulfate reagent solution in addition to the Bicinchoninic Acid (BCA) reagent solution.
Response: Comment not incorporated. It is standard *USP–NF* monograph style to include the formulae for particular reagents and if possible provide a footnote with sources for more complicated mixtures where it may be helpful. Analysts are still able to use vendor prepared reagents that match a particular formula even without a footnote.
Comment Summary #19: The commenter suggested some revision to the BCA procedure in Method II text based on their procedure.
Response: Comment not incorporated. The method was validated as written. Alternative procedures are allowed per *General Notices*, see Comment Summary #1.
Comment Summary #20: The commenter suggested that an alternative protein concentration range should be added to this section for lower protein concentrations.
Response: Comment not incorporated. The method was validated as written. The Expert Committee will consider future revisions to the General Chapter, upon the receipt of the necessary supporting data. In addition, alternative procedures are allowed per *General Notices* 6.30 as discussed in Comment Summary #1.

Comment Summary #21: The commenter stated that BCA works better with basic pH samples and suggested revisions that recommended alternative buffer systems.
Response: Comment not incorporated. The Expert Committee understands that this may be possible, but there are many special cases for every analytical method and the General Chapter method covers the most common sample types. In all cases, users must verify that the compendial method is suitable for their particular purposes and develop and validate an alternative method if verification fails.
Comment Summary #22: The commenter recommended the Note regarding the use of microplates and volume adjustments include an example of volumes that may be suitable.
Response: Comment not incorporated. Users may use multiple types of microplates with varying volumes and it is up to the user to demonstrate the suitability of their volume choices for their particular plate and plate reader

Method III. Bradford Method
Comment Summary #23: The commenter requested deletion of the text for mixing by inversion in case users were using microplates.
Response: Comment not incorporated. The method was validated as written and the particular volumes shown were most suitable and therefore test tube based. Alternative procedures are allowed per *General Notices* 6.30 as discussed in Comment Summary #1.
Comment Summary #24: The commenter recommended deletion of the text regarding the use of quartz cuvettes and autozeroing the instrument from both subsections, because it is redundant.
Response: Comment not incorporated. The Expert Committee believes that the instruction should remain in both subsections A and B, because if a user was just following one of the subsections then they may miss the critical instruction if it were removed.

Method IV. Lowry Method
Comment Summary #25: The commenter stated alternative methods such as plate-based could be added to this section.
Response: Comment not incorporated. The method was validated as written and the laboratory was not able to match the sensitivity requirements with a plate-based method. In addition, alternative procedures are allowed per *General Notices* 6.30 as discussed in Comment Summary #1.

Method V. Amino Acid Analysis
Comment Summary #26: The commenters indicated that alternative amino acid analyses methods and separation procedures could be used rather than just the one shown in the General Chapter and suggested some text edits.
Response: Comments not incorporated. The method shown was validated for multiple proteins and found suitable. Alternative procedures are allowed per *General Notices* 6.30 as discussed in Comment Summary #1. The validated method shown is not required for a laboratory to use unless a monograph for a particular drug substance or product cites the General Chapter.
Comment Summary #27: The commenter indicated that the text, “which may be a helpful but not mandatory resource” should be deleted, because General Chapter <1052> *Biotechnology-Derived Articles–Amino Acid Analysis* is required for a complete description of the method.
Response: Comment not incorporated. General Chapter <1052> is an information chapter that contains helpful information and common starting points for amino acid methods. If users

decided to use one of the methods in General Chapter <1052> then full validation (not just verification) would be required. Because the methods in General Chapter <1052> are not sufficient for a user to adopt and verify, the Note described in General Chapter <507> is important to clarify the intent of citing General Chapter <1052>.
Comment Summary #28: The commenter recommended deleting the hydrolysis section and to cite the many hydrolysis procedures in General Chapter <1052> instead.
Response: Comment not incorporated. In addition to the response to Comment Summary #27 regarding the suitable use of General Chapter <1052>, the method was validated as written. Alternative procedures are allowed per *General Notices* 6.30 as discussed in Comment Summary #1.
Comment Summary #29: The commenter suggested providing the linear working range for each amino acid in the sentence, "Prepare a protein sample such that the content of amino acids is within the established linear working range of the procedure."
Response: Comment not incorporated. Suggestions for suitable amino acid concentrations are already provided in the *Standard solution section*. In addition, the linear range could vary somewhat based on instrumentation and particular protein and the laboratory verifying the method for their purpose will have to demonstrate it is suitable for their purpose.
Comment Summary #30: The commenter recommended adding a statement that alternative commercially available hydrolysis tubes could be used because the flame sealable type can be difficult to seal and can break. Additionally, some of the sealing text is very specific to sealing just this type of tube.
Response: Comments incorporated. The following Note was added: "Note- Alternative commercially available hydrolysis vials can also be used.
Comment Summary #31: The commenter requested clarification of the calculation for the Relative standard deviation (RSD) of NMT 2.0% in the *System suitability* section.
Response: Comment not incorporated. The method cites General Chapter <621> *Chromatography* for system suitability guidance. Users can consult this General Chapter for further guidance on these requirements.
Comment Summary #32: The commenters requested clarification of the use of the method for unknown protein samples versus known and defining well recovered amino acids.
Response: Comments incorporated. The purpose of the method was revised to be for proteins of known molecular weight and amino acid composition and deleting text that supported its use for the more complex applications of unknown proteins. In addition, a *Note* was added to the *Calculations* section so that readers know that more helpful guidance on this topic can be found in the *Protein Hydrolysis* section of General Chapter <1052> , which provides guidance on well recovered amino acids,
Expert Committee-initiated Change #1: The following revision was made to the introduction to *Method 1A* and Method *1B*, "Depending on the protein <u>structure and the nature of the protein</u> sample (e.g., <u>denaturing conditions may be more suitable for</u> a strong coiled structure with …"
Expert Committee-initiated Change #2: The following revision was made in the *Standard solution*s instructions found in *Method II* and *Method III*, "If ~~either~~ the protein of interest is unknown, is a mixture, or is a specific…"

General Chapter/Sections:	<791> pH/Multiple Sections
Expert Committees:	General Chapters—Chemical Analysis
No. of Commenters:	2

General
Comment Summary #1: The commenter recommended clarifying the usage of the term "calibration" in the General Chapter and adding a statement regarding the frequency of calibration.
Response: Comment not incorporated. The revision harmonizes terminology for consistency with other pharmacopoeias without changes to the calibration procedures. Frequency of calibration is outside of the scope of this General Chapter.

Calibration
Comment Summary #2: The commenters requested reviewing the range of the typical acceptable parameters for the slope of the two point calibration of 90.0-105.0% to 90-105% and for the offset of 0.0±30 mV to 0±30 mV.
Response: Comments incorporated.

General Chapter/Sections:	<1050.1> Design, Evaluation, and Characterization of Viral Clearance Procedures/Multiple Sections
Expert Committee:	General Chapters—Biological Analysis
No. of Commenters:	5

General Comments
Comment Summary #1: The commenters requested clarifications to the figures regarding sampling steps versus process flow steps and the use of filters in *Figure 2*.
Response: Comments incorporated within the figures and associated figure legend text. In addition, the text below F*igure* 2 provides guidance regarding the use of filters.
Comment Summary #2: The commenters requested addition of several publications and questioned if all guidance was current.
Response: Comments partially incorporated. The sentence "USP encourages readers to maintain and keep current best practices in the field by reviewing current peer reviewed publications, regulatory guidance, and key opinion leaders and organizations." It is beyond the scope of a USP informational general chapter to provide a complete literature review that will change over time. The Expert Committee determined that the General Chapter is aligned with current best practices.

Goals and Principles of Viral Clearance Studies
Comment Summary #3: The commenter requested that the term Log Reduction Value or LRV also be mentioned where VRF and LRF are defined.
Response: Comment incorporated.
Comment Summary #4: The commenter indicated that the section text applied commercial standards to all viral clearance studies.
Response: Comment not incorporated. The informational general chapter contains best practices and already provides phase-specific guidance in other sections.
Comment Summary #5: The commenter suggested revision of the text as follows, "Critical attributes of strategic viral clearance steps in the manufacturing process must be characterized ~~and validated,~~" because validation applies to the scaled down model.
Response: Comment incorporated.
Comment Summary #6: The commenter requested adding the underlined text, "1) the ability of process steps to remove <u>and/</u>or inactivate viruses under…"

Response: Comment incorporated.
Comment Summary #7: The commenter thought that a word was missing in a sentence and proposed a revision to the text.
Response: Comments incorporated. The underlined word was added, "…consistently remove or inactivate nonspecific viruses that possess a broad spectrum of physical and chemical resistance characteristics…"

Considerations for Performance of Viral Clearance Studies
Comment Summary #8: The commenter suggested adding examples of the type of viruses that should be used in clearance studies.
Response: Comment incorporated. The underlined text was added, "In general at least two viruses, one enveloped (typically a retrovirus, e.g., MuLV) and one non-enveloped (preferably a parvovirus, e.g., MVM), are used…"
Comment Summary #9: The commenter suggested adding the underlined text for clarification, "At least two orthogonal virus removal/inactivation steps (steps with different mechanisms of clearance should be evaluated per virus."
Response: Comment incorporated.
Comment Summary #10: The commenter requested revisions to the text to clarify how the use of in-house data could support reproducibility for a specific model system.
Response: Comment incorporated. The text was modified to state, "The reproducibility of an effective step should be assessed by performing at least two independent experiments, or reproducibility should be supported by the process development history (or experiences). ~~relevant in-house data.~~"
Comment Summary #11: The commenter proposed a correction: "…or of the same species as ~~viruses of~~ the virus that is known, or likely to…"
Response: Comment incorporated.
Comment Summary #12: The commenter requested that "high" should be changed to "very high" for resistance of parvoviruses in Table 1.
Response: Comment incorporated.
Comment Summary #13: The commenter asked for consistent use of LRF or LRV as opposed to "logs" in the *Process Clearance Capability* subsection
Response: Comment incorporated.
Comment Summary #14: The commenter asked for the source of the >4 LRF clearance value and stated that in their experience it was usually 8-10.
Response: Comment partially incorporated. The term "minimum" was added to the sentence: "Minimum clearance capability for other types of viruses might include…" This value can vary by product and 8-10 LRF is not possible for some types of products.
Comment Summary #15: The commenters requested clarification regarding the 95% confidence interval statement and how this is performed.

Response: Comments incorporated. The following edits were made, “In general for a single clearance step to be considered effective, 4 LRF ~~logs~~ or more of clearance must be demonstrated ~~with 95% confidence (a=0.05)~~. In contrast, a clearance step demonstrating 1-3 LRF ~~logs of clearance with 95% confidence (a=0.05)~~ is considered a supportive step. The titer of the virus input and output for any given process step evaluated should include 95% confidence (a=0.05). A step can be supportive for some viruses and effective for others. When possible and as process knowledge allows ~~To avoid overestimating reduction capacity~~, the analyst should...”

Comment Summary #16: The commenter suggested the following correction to the text, “Comparability should be demonstrated using representative raw materials and ~~in~~ intermediates…”

Response: Comment incorporated.

Comment Summary #17: The commenter suggested the following modifications to the text to show that the parameters are examples, “For chromatography, the ~~following~~ parameters should be representative of the respective clinical or commercial-scale manufacturing (e.g., the column bed height, residence time…”.

Response: Comment incorporated.

Comment Summary #18: The commenter suggested the following edits to the text, “Scaled-down and manufacturing-scale chromatography systems should produce similar elution profiles ~~and~~, step yields and final product analytical profile (e.g. SEC-HPLC and/or SDS-PAGE analyses)”

Response: Comment incorporated.

Comment Summary #19: The commenter indicated that it was unclear why a sample might be diluted before storage rather than only before assay.

Response: Comment not incorporated. Some samples may have interference that should be diluted before storage and some inactivation can occur during storage depending on the sample matrix composition. Appropriate controls are critical.

Comment Summary #20: The commenter indicated that the serial dilution examples of 10-fold, 5-fold-, or 2-fold should not be included, because they might be too restrictive.

Response: Comment not incorporated. As written in the text, these dilutions are helpful suggestions and examples already, not requirements.

Comment Summary #21: The commenter indicated that it was unclear why the General Chapter emphasized establishing the certified titer of virus stocks.

Response: Comment not incorporated. The certified titer is needed for toxicology studies and it also confirms that your input (spike) matches your output result later.

Comment Summary #22: The commenter indicated that the requirement, “Analysts should perform a mock spiking study before the true spiking study” was unnecessary and that resources are better spent on challenging process parameters.

Response: Comment partially incorporated. The sentence as written was never a requirement and uses the word “should.” The Expert Committee determined the exercise can add value, but agrees it is not a required and modified the statement as follows, “It may be advisable to ~~analysts should~~ perform a mock…”

Comment Summary #23: The commenter recommended clarifying the use of stabilizing protein in mock spiking studies.

Response: Comment not incorporated. Stabilizing protein was shown only as an example of the types of additives that might be present and should be considered.

Comment Summary #24: The commenter stated that in the *Viral Clearance by Filtration* section it is not common practice to use the hold control in calculations and asked for a clarification of the sentence.
Response: Comment incorporated. The following revision was made to the text, "The virus titers obtained from the spiked load and hold control should be within the experimental variability of the virus titration assay ~~and if so, the analyst can average these values to obtain the initial virus load for use in calculating log reduction value~~."
Comment Summary #25: The commenter asked for clarification of how "evidence of constant viral clearance after multiple uses" could be defined
Response: Comment incorporated. The incorrect word "constant" was replaced with "consistent."
Comment Summary #26: The commenter requested edits to the text regarding testing samples immediately versus freezing.
Response: Comment incorporated. The following edit was made to the text, "The spiked load control ~~should be tested immediately for virus titer,~~ and additional samples should be tested immediately ~~as soon as possible~~ or immediately frozen."
Comment Summary #27: The commenters had similar questions in the *Viral Clearance by Column Chromatography* as found in Comment Summary #24, regarding the use of the hold control in calculations.
Response: Comments incorporated. The following sentence was deleted, "The titer of the hold control or an average of the titers of hold control and spiked load (if within assay variability) should be used as the starting titer in the viral clearance calculation."

General Chapter/Section(s): <1065> Ion Chromatography/Multiple Sections
Expert Committee: General Chapters—Chemical analysis
No. of Commenters: 3

Introduction
Comment Summary #1: The commenter indicated that the statement second sentence of the paragraph, "A not exhaustive list may include…," was confusing way to start the list of items and suggested rewording the statement.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended noting that, "Without significant sample cleanup, ion chromatography may be challenging for samples in high ionic strength matrices, since the salt in the sample may interfere with analyte retention and/or conductivity detection."
Response: Comment not incorporated. It is not possible to define how much is significant and what is the nature of clean-up. The need and extension of clean-up is matrix dependent and should not be a general statement.

Apparatus
Comment Summary #3: The commenter suggested revising the section to clarify that conventional HPLC instruments can be used as Ion Chromatography (IC) instruments. Therefore they suggested changing the wording to provide this alternative.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended including the following language in the text: "…a metal free system should be used for trace analysis or when acidic mobile phases are employed."

Response: Comment not incorporated. The current proposal is associated with limitations for metal ion analysis as a consequence of metal release from the system. The comment is outside the scope of the General Chapter.

Mobile Phases

Comment Summary #5: The commenter indicated that in the text "…a wide variety of salt solutions may be used for into the mobile phase," the use of the phrase "used into" was confusing and suggested changing to a provided alternative.

Response: Comment incorporated.

Comment Summary #6: The commenter indicated that mobile phases are typically referred as "eluents" in Ion Chromatography.

Response: Comment was not incorporated. USP adopts the nomenclature (IUPAC) "Chromatography is a physical method of separation in which the components to be separated are distributed between two phases, one of which is stationary (stationary phase) while the other (the mobile phase) moves in a definite direction."

Comment Summary #7: The commenter recommended including additional discussion that contamination of eluents with carbonate ion can be particularly troublesome when using alkaline mobile phases. Carbonate contamination can be minimized through use of high purity alkali reagents and storage under nitrogen or helium headspace.

Response: Comment incorporated.

Stationary Phases

Comment Summary #8: The commenter indicated that in the sentence "…that sometimes are needed into the mobile phase …" the use of the phrase "needed into" is confusing and suggested an alternative.

Response: Comment incorporated.

Comment Summary #9: The commenter recommended additional discussion that a polymeric support for IC is useful over an extended pH range, although efficiency and peak symmetry may be somewhat reduced in polymer-based separators relative to silica-based columns.

Response: Comment not incorporated. The problem of silica matrix is the solubility in alkaline solutions, which is explained in the General Chapter. The thermodynamics of peak symmetry is outside the scope of this General Chapter.

General Chapter/Sections: <1207> Package Integrity Evaluation—Sterile Products
Expert Committee: General Chapters—Microbiology
No. of Commenters: 12

Title

Comment Summary #1: The commenter recommended changing the title of the General Chapter to better reflect its content

Response: Comment incorporated.

Introduction

Comment Summary #2: The commenter recommended omitting the following sentence, because it is outside the scope of sterility, "These contaminants include microorganisms, but may also include reactive gases or other substances."

Response: Comment not incorporated. The General Chapter's intent is to provide guidance on the means to assure integrity of packages intended to contain sterile products. Integrity concerns go beyond microbial contamination.
Comment Summary #3: The commenter suggested clarifying that integrity from particulate matter must be ensured for auto-injector assembly, but not the auto-injector itself.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended omitting the reference to "specified water vapor content" as it relates to headspace content preservation.
Response: Comment not incorporated. Water vapor barrier is a package integrity requirement for some products.
Comment Summary #5: The commenter recommended clarifying the definition of non-porous, because the bags are gas permeable.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended adding specificity and robustness to the validation elements.
Response: Comment incorporated.
Comment Summary #7: The commenter recommended clarifying allowable limits for ingress
Response: Comment incorporated.
Comment Summary #8: The commenter recommended adding more detailed recommendations for the selection, qualification, and use of leak test methods.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested clarifying the intent of the General Chapter.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested indicating that science and risk based testing should be leveraged.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested adding medical devices to the scope of the General Chapter.
Response: Comment not incorporated. At this time medical devices are outside the scope of the General Chapter; however, the Expert Committee will continue to consider the possibility of including medical devices (and other product types) intended to provide sterility assurance to sterile products.

Scope
Comment Summary #12: The commenter recommended clarifying the types of sterile products that are covered by this General Chapter and those that are excluded.
Response: Comment incorporated.
Comment Summary #13: The commenter recommended clarifying whether pre-sterilized container closure components are within the scope of the General Chapter.
Response: Comment incorporated.

Leak and Leakage Rate
Comment Summary #14: The commenter recommended clarifying the differential pressures that can be used during testing (e.g. reference to ISO II242).

Response: Comment not incorporated. Some leak tests mandate specific differential pressures that must be used to elicit a measured leakage response. Use of the standards referenced remains the responsibility and decision of the drug product manufacturer.
Comment Summary #15: The commenter recommended changing the term "leakage" to "leakage rate" when referring to a rate.
Response: Comment incorporated.
Comment Summary #16: The commenter recommended including IUPAC standard units of measure.
Response: Comment not incorporated. The text was revised to refer to the appropriate reference sources for units of measure.
Comment Summary #17: The commenter suggested revising the text to indicate that leakage is not always gas flow, and leakage in a dye test is defined as a volume of dye solution penetrating a container.
Response: Comment incorporated.

Product-Package Quality Requirements and Maximum Allowable Leakage Limit
Comment Summary #18: The commenter suggested that the text include a temperature range for ultra-cold.
Response: Comment incorporated.
Comment Summary #19: The commenter indicated that the General Chapter should specify that vapor content can be derived from the formulation in equilibrium with its headspace.
Response: Comment not incorporated. The Expert Committee agrees with the point made; however, water vapor rise has been found to result from ingress of air, including water vapor.

Definitions
Comment Summary #20: The commenter recommended omitting definitions from the General Chapter
Response: Comment not incorporated. Definitions are placed in the introductory chapter, as recommended by stakeholders.
Comment Summary #21: The commenter suggested that the definition of Probabilistic Leak Test Method be clarified.
Response: Comment incorporated.
Comment Summary #22: The commenter suggested adding a definition on system suitability
Response: Comment incorporated.
Comment Summary #23: The commenter suggested discussing the difference between master reference standard and negative control.
Response: Comment incorporated.
Comment Summary #24: The commenter suggested that the definition of microbial challenge test be revised to state, "Leakage is evidenced by the subsequent growth of the challenge microorganisms in the package contents."
Response: Comment incorporated.
Comment Summary #25: The commenter recommended changing the term “Acceptance criterion" to "pass/fail limit,” because pass/fail is used throughout the General Chapter.
Response: Comment incorporated.
Comment Summary #26: The commenter recommended aligning the nonporous packaging definition with medical device standards.
Response: Comment incorporated.

Comment Summary #27: The commenter suggested aligning the definition on precision with ICH Q2.
Response: Comment incorporated.

General Chapter/Sections: <1207.1> Package Integrity Testing in the Product Lifecycle: Test Methods Selection and Validation
Expert Committee(s): General Chapters—Microbiology
No. of Commenters: 12

General
Comment Summary #1: The commenter recommended clarifying whether porous barrier packages are within the scope of the General Chapter.
Response: Comment incorporated.

Package Integrity Testing in the Product Life Cycle
Comment Summary #2: The commenter recommended adding a statement from the FDA regarding the use of products integrity tested for other tests during stability.
Response: Comment not incorporated. The text was revised to more clearly reference FDA guidance.
Comment Summary #3: The commenter suggested that the statement, "Development efforts should include studies that evaluate package integrity at the extremes of the finished product–package profile, not simply at optimal conditions," is not practical. Vendors/suppliers will not likely be able to provide components at the extreme ranges of the specification to meet the proposed expectation, so the sentence should be revised.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended referencing the FDA's 2008 *Guidance for Industry: Container and Closure System Integrity Testing In Lieu of Sterility Testing.*
Response: Comment incorporated.
Comment Summary #5: The commenter suggested that container closure integrity testing during routine manufacturing is not a requirement and indicated that the text should clarify why this would be considered during development.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended mentioning stack-up tolerances for multicomponent systems.
Response: Comment incorporated.

Test Method Criteria
Comment Summary #7: The commenter recommended replacing this section with a decision tree to guide the reader through options.
Response: Comment not incorporated. A comprehensive, easy-to-read decision tree including all options was found to be impractical given the many product-packages and testing options available.
Comment Summary #8: The commenter recommended inserting guidance on how to simulate movement (e.g. plunger in syringes) for movable components.
Response: Comment not incorporated. It is not the intent of the General Chapter to include details of test sample set-up.

Comment Summary #9: The commenter suggested inserting guidance or examples for opaque material.
Response: Comment not incorporated. The General Chapter will not provide guidance on opacity as it relates to leak test method capability. This is determined by the end-user on a case-by-case basis.
Comment Summary #10: The commenter recommended adding the bubble emission test as a potential test method
Response: Comment not incorporated. This test is outside the scope of the General Chapter.
Comment Summary #11: The commenter recommended having a table outlining the benefits/limitations of the various methods versus container type.
Response: Comment incorporated.
Comment Summary #12: The commenter recommended the addition of examples of the various multidose product types in the section on *Multidose Product, Microbial Blockage Closure Systems*.
Response: Comment incorporated.
Comment Summary #13: The commenter recommended adding a footnote, or comment in the *Leak size* and *Leakage rate* table to clarify that the ranking is not a measure of better/worse.
Response: Comment incorporated.
Comment Summary #14: The commenter recommended adding examples to the section regarding headspace preservation methods.
Response: Comment incorporated.
Comment Summary #15: The commenter recommended adding guidance on when 100% nondestructive leak testing is preferred.
Response: Comment incorporated.
Comment Summary #16: The commenter recommended adding information about the smallest leak detection required (e.g., requirement given for the package development phase - 0.1 - 0.2 um in nominal diameter) for the three product categories.
Response: Comment incorporated.
Comment Summary #17: The commenter recommended removing 0.1um as smallest limit for microbial ingress. B.diminuta is not smaller than 0.2um. Using a method with a 0.2 limit would not affect the outcome in terms of microbiological safety.
Response: Comment incorporated.
Comment Summary #18: The commenter recommended that the section describing probabilistic methods be reworded with a more balanced approach focusing on selection of method based on product type.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested revising the table on *Determining LOD* for methods because it is confusing.
Response: Comment incorporated.
Comment Summary #20: The commenter suggested that the *Limit of detection* should not be required with every routine test once established/validated. Positive and negative controls must be included with every routine test. It is not required that the controls be run at the validated LOD level.
Response: Comment incorporated.
Comment Summary #21: The commenter suggested that the text specify that with certain test methods, such as helium leak/vacuum decay, the largest leak could be a concern. For other methods, it is not.

Response: Comment incorporated.
Comment Summary #22: The commenter recommended that it be clarified that the intent of leak detection as part of batch manufacturing is to support routine manufacturing or an assessment at the developmental stage.
Response: Comment incorporated.
Comment Summary #23: The commenter suggested that the establishment of a range is part of validation and should not be included in routine container closure integrity testing.
Response: Comment incorporated.
Comment Summary #24: The commenter recommended adding considerations regarding the challenges of online methods (e.g. placement of the test, detection of small leaks over time).
Response: Comment incorporated.
Comment Summary #25: The commenter suggested emphasizing that no single method is appropriate for all packages.
Response: Comment incorporated.
Comment Summary #26: The commenter recommended explaining the differences between direct and tortuous paths and their associated critical holes size limits.
Response: Comment incorporated.

Test Instrument Qualification, Method Development and Method Validation
Comment Summary #27: The commenter recommended simplifying this section to state that comparison of a physicochemical test method to a microbial method is no longer required.
Response: Comment not incorporated. The text was revised and now explains situations in which microbial ingress comparisons may be and may not be useful.
Comment Summary #28: The commenter recommended adding a caveat that a positive control in routine use does not have to be run to the method's limit of detection.
Response: Comment not incorporated. System suitability text was added that includes a discussion of positive/negative controls usage.
Comment Summary #29: The commenter recommended distinguishing between precision and intermediate precision (days, labs, operators, instruments).
Response: Comment incorporated.
Comment Summary #30: The commenter suggested checking the General Chapter to make sure the terms positive and negative controls are applied appropriately.
Response: Comment incorporated.
Comment Summary #31: The commenter suggested that grow through is not truly a container closure integrity issue and should be omitted from the chapter.
Response: Comment incorporated.
Comment Summary #32: Commenter suggested that not all parameters need to be varied but that the procedural parameters that affect the test result in the biggest way are known or determined during development.
Response: Comment incorporated.
Comment Summary #33: The commenter recommended adding text around what can be done to confirm system suitability.
Response: Comment incorporated.
Comment Summary #34: The commenter recommended the removal of all editorial comments comparing microbial ingress to deterministic methods, because historical practice has been based on microbial methods and is demonstrated to be effective

Response: Comment not incorporated. The new text explains situations in which microbial ingress comparisons to physicochemical methods may be and may not be useful. No method has been or can be demonstrated to be effective for all product-packages for all use situations.

General Chapter/Sections: <1207.2> Package Integrity Leak Test Technologies
Expert Committee(s): General Chapters—Microbiology
No. of Commenters: 7

General
Comment Summary #1: The commenter suggested that the information in the General Chapter would be more suitable as a review article in an alternate location (e.g. Stimuli).
Response: Comment not incorporated. General Chapters are updated routinely, so keeping the information in a General Chapter will better ensure current information to users.
Comment Summary #2: The commenter recommended the inclusion of a decision tree. This would help guide users in using the General Chapter.
Response: Comment not incorporated. A comprehensive, easy-to-read decision tree including all options was found to be impractical given the many product-packages and testing options available.
Comment Summary #3: The commenter suggested including the microbial dusting technique in the General Chapter.
Response: Comment not incorporated. Only microbial immersion by liquid challenge was judged to be potentially sensitive enough to identify leaks that risk sterile pharmaceutical product sterility loss.

Table 1
Comment Summary #4: The commenter recommended clarifying tests that may be destructive under certain cases.
Response: Comment incorporated.
Comment Summary #5: The commenter recommended clarifying that tests are product-package specific.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended allowing IR light transmission to package requirement of laser-based headspace analysis.
Response: Comment incorporated.

Table 2
Comment Summary #7: The commenter recommended clarifying that the tests may be destructive under certain cases.
Response: Comment incorporated.

Tracer Gas Detection, Vacuum Mode
Comment Summary #8: The commenter recommended changing the tracer gas detection range to 1–5.
Response: Comment incorporated.

Microbial Challenge, Immersion Exposure
Comment Summary #9: The commenter suggested that many companies have validated shorter incubation times (e.g., 5 - 7 days) which are more typically for test strains such as B. diminuta. Text should be revised to reflect this point.
Response: Comment incorporated.
Comment Summary #10: The commenter recommended adding a cautionary statement regarding the ability of the media to support growth of the microorganism over long periods of time.
Response: Comment incorporated.

Tracer Gas Detection, Sniffer Mode
Comment Summary #11: The commenter recommended changing the Tracer Gas detection, Sniff mode range to 2 – 6.
Response: Comment incorporated.

General Chapter/Sections: <1207.3> Package Seal Quality Test Technologies
Expert Committee(s): General Chapters—Microbiology
No. of Commenters: 3

General
Comment Summary #1: The commenter suggested that the information in the General Chapter is not consistent with related information found in <1207> *Sterile Product Packaging—Integrity Evaluation*. Therefore, it was recommended to address inconsistency.
Response: Comment incorporated.

Closure Application and Removal Torque
Comment Summary #2: The commenter suggested that consideration should be given to min/max forces for special populations that may not be able to exert much force, yet need to open and properly close caps to make a proper seal.
Response: Comment incorporated.

Package Seal Strength
Comment Summary #3: The commenter suggested that the ASTM F2884 method should be added to the chapter.
Response: Comment not incorporated. ASTM F2884 does not deal the product-packages.

Package Burst
Comment Summary #4: The commenter suggested that the purpose of the *Burst Test* is to challenge the seal and not the package surface area or the tooling contact surface. Text should be revised to reflect this point
Response: Comment incorporated

General Chapter/Sections: <1228> Depyrogenation
Expert Committee: General Chapters—Microbiology
No. of Commenters: 3

Comment Summary #1: The commenter recommended clarifying that the scope of this General Chapter to state that it covers the depyrogenation process for both product stream and equipment/container closure, for improved clarity.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested clarifying that the degree of adsorption of or aggregation of the purified LPS molecule is affected by a host of matrix attributes to which it is exposed.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested clarifying how or why Naturally Occurring Endotoxin may be used in depyrogenation process validation.
Response: Comment incorporated.
Comment Summary #4: The commenter indicated that the phrase "choose a preparation with no fillers" is not clear, and suggest rephrasing for improved clarity.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested that the level of challenge material should be established taking into account the formulation matrix, as the matrix itself may add considerable variability to the outcome of the study, the log reduction or safety level target, and the efficiency of the extraction method.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested clarifying how an understanding of the characteristics of the material is important in the depyrogenation process.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested clarifying the points on preparation of test samples such as affixing, drying and recovery of endotoxins.
Response: Comment incorporated.
Comment Summary #8: The commenter recommended addition of text to indicate that different depyrogenation processes have different efficiencies both within and between treatment types.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested clarifying why a uniform requirement for a depyrogenation process, such as a 3 log reduction of endotoxin load, may not be appropriate for all materials.
Response: Comment incorporated
Comment Summary #10: The commenter suggested including that the depyrogenation process should be able to handle the worst endotoxin load
Response: Comment incorporated.
Comment Summary #11: The commenter suggested clarifying that exercising control over endotoxin content of incoming materials can be achieved by monitoring incoming materials and control of in-process microbial growth and therefore reduce or eliminate the need for endotoxin removal downstream.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested clarifying that qualification of primary packaging component suppliers should include an audit that confirms the consistent control over the applicable manufacturing processes.
Response: Comment incorporated.
Comment Summary #13: The commenter recommended including specific information on indirect measures of endotoxin control. Although they may be implied, they are never identified as such in the text.

Response: Comment incorporated.
Comment Summary #14: The commenter indicated that validation during performance qualification (PQ) should use the worst-case parameters.
Response: Comment incorporated.
Comment Summary #15: The commenter suggested that "reproducibility" is an important aspect in performance qualification and should be included in performance qualification.
Response: Comment incorporated.
Comment Summary #16: The commenter suggested some depyrogenation processes are continuous (i.e. dry heat tunnel) and not linked to a cycle; therefore, critical parameters of the process should be monitored for routinely for such a process.
Response: Comment incorporated.

General Chapter/Sections: <1228.1> Dry Heat Depyrogenation
Expert Committee: General Chapters—Microbiology
No. of Commenters: 10
Comment Summary #1: The commenter expressed concern regarding the statements in the General Chapter proposal that suggest the use of endotoxin indicators are not necessary for validation dry heat depyrogenation processes that yield FH values >30 minutes during the exposure period. While annual requalification studies designed to demonstrate that depyrogenation equipment continues to operate within validated parameters should routinely use endotoxin indicators, the most robust methods may not always require endotoxin indicators. Specifically, if a process uniformly achieves accumulate F_H values >30 minutes measured at temperatures of 250 degrees or higher, only periodic endotoxin challenges (e.g., every three years) may be needed to confirm that endotoxin destruction/inactivation is achieved. However, in cases where changes to the depyrogenation process require revalidation, use of endotoxin indicators would also be recommended for revalidation studies (but not each subsequent requalification study).
Response: Comment incorporated.
Comment Summary #2: The commenter suggested that the lower end of the typical temperature for depyrogenation be changed from 170 degrees to 160 degrees to be in line with the corresponding general chapter in the European Pharmacopoeia.
Response: Comment not incorporated. The Expert Committee determined that this is not necessary, because this General Chapter is about depyrogenation and not sterilization.
Comment Summary #3: The commenter suggested clarifying that the well-defined kinetics of inactivation makes it possible to predict the efficacy of dry heat processes operating at different times and temperatures by understanding the total thermal input (FH).
Response: Comment incorporated.
Comment Summary #4: The commenter suggested clarifying that it is possible that the control probes may not achieve the set-point temperature. In order to ensure sufficient lethality and process control, oven control probe(s) must maintain a predefined temperature for a predefined time period prior to cooling.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested clarifying that the use of tunnels for dry heat depyrogenation of glass containers on a moving conveyor allows for substantially higher throughput and packing densities than the batch process, presents the containers to a stabilized process rather than an on/off process such as the batch process, and is generally integrated with washing and filling system.

Response: Comment incorporated.
Comment Summary #6: The commenter suggested clarifying that load items in tunnels are typically fed from an integrated container washing system directly onto the conveying system.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested changing the term "mass/geometry" to "mass per unit area."
Response: Comment incorporated.
Comment Summary #8: The commenter proposed that the term “FH” is reserved to dry-heat sterilization and that F calculation for dry-heat depyrogenation is referred to as “F_D”. While calculations are the same, the references values may differ since the purpose is different in the 2 situations.
Response: Comment incorporated.
Comment Summary #9: The commenter recommend that additional text be added to clearly state that 50^0 is specified only as an example for the purposes of demonstrating how to perform the calculations, and that other z-values can be used.
Response: Comment incorporated.
Comment Summary #10: The commenter noted that the statement suggesting that a process demonstrating an F_H of 30 min during the exposure period can be considered extremely safe in terms of pyrogen inactivation may be true only if the temperature mapping of the loaded oven has demonstrated even heat distribution.
Response: Comment incorporated. Statement deleted.
Comment Summary #11: The commenter proposed correcting formula and descriptions to be consistent with integrating thermal input across the entire time and temperature range of exposure-not limited to 250C.
Response: Comment incorporated.
Comment Summary #12: The commenter indicated that the empty chamber temperature distribution evaluation is best performed over the last few minutes of the dwell period once the system has fully stabilized.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested that the acceptance criteria for empty chamber temperature distribution evaluation varies with the oven's capabilities and customary usage, however, temperature distribution is typically substantially less uniform than observed in other thermal sterilization processes and may be ±15 degrees or more.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested clarifying for depyrogenation tunnels, because temperature studies under fully loaded conditions only are indicated.
Response: Comment incorporated.
Comment Summary #15: The commenter noted that the statement suggesting that a process demonstrating an F_H of 30 min during the exposure period can be considered extremely safe in terms of pyrogen inactivation may be true only if the temperature mapping of the loaded oven has demonstrated even heat distribution.
Response: Comment incorporated.
Comment Summary #16: The commenter suggested adding that a critical aspect to the proper operation of the dry heat tunnel is establishing the required air flow balance between the tunnel and the adjoining areas. Improper air flow can cause uneven heating across the load being processed.
Response: Comment incorporated.

Comment Summary #17: The commenter suggested clarifying that all load items should be prepared and oriented in a manner consistent with how they will be processed.
Response: Comment incorporated.
Comment Summary #18: The commenter suggested that for tunnel depyrogenation studies, glass formats may be different and should be mapped.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested clarifying that glass temperature can be assessed using sets of calibrated temperature sensors (i.e., trailing or wireless temperature sensor) positioned within the glass pack as it moves through the tunnel. Temperature sensor should be placed into direct contact with the item(s) at the bottom of the container.
Response: Comment incorporated.
Comment Summary #20: The commenter recommended deleting the term "parametric controls" and clarifying this statement because the use of this term in routine process control is confusing.
Response: Comment incorporated.
Comment Summary #21: The commenter recommended that the incoming material be evaluated and the endotoxin threshold specified. The commenter also recommended initial endotoxin evaluation and routine validation of the depyrogenation process. Further, if the endotoxin level has changed, a new revalidation may be required.
Response: Comment incorporated. Text was added.
Comment Summary #22: The commenter recommended adding the following reference to the *References* section of the General Chapter. *Technical Report No.* 3 (revised 2013), *Validation of Dry Heat Processes Used for Depyrogenation and Sterilization*.
Response: Comment incorporated.

General Chapter/Sections: <1229.5> Biological Indicators for Sterilization
Expert Committee: General Chapters—Microbiology
No. of Commenters: 2
Comment Summary #1: The commenter suggested including a section on biological indicators (BIs) for decontamination.
Response: Comment not incorporated. The Expert Committee determined that the inclusion of decontamination related content in this General Chapter would cause confusion.
Comment Summary #2: The commenter suggested use of consistent terminology to describe bioburden and define the chosen term.
Response: Comment incorporated. Multiple changes were made to the text to reflect this comment.
Comment Summary #3: The commenter recommended clarifying if the "survival time" and "kill time" should be included with the "D and Z value" determination as part of the BI manufacturer's responsibility.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested adding a reference to General Chapter <55> and directing the user to verify the label claim.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested including G. stearothermophilus as a commonly used BI for moist heat sterilization of aqueous liquids, because it is widely used as a BI for this purpose.

Response: Comment not incorporated. The Expert Committee determined that the use of G. stearothermophilus in terminal sterilization is rarely justifiable. Its extreme resistance results in products being aseptically processed that might otherwise be terminally sterilized using a more appropriate BI due to the excessive time-temperature required to kill G. stearothermophilus.
Comment Summary #6: The commenter suggested changing the reference for *Dry Heat Sterilization* from <1229.7> *Gaseous Sterilization* to <1229.8> *Dry Heat Sterilization*.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested that "confirm" is the better word choice because "reconfirm" implies something has already been done. Where dry heat depyrogenation has been validated, sterilization need not be confirmed. Also suggested the addition of explanation of why sterilization validation is not needed if depyrogenation has been demonstrated. This could be helpful to the reader who does not realize that the depyrogenation temperatures needed to inactivate endotoxins are so high that they sterilize as well.
Response: Comment incorporated.
Comment Summary #8: The commenter suggested considering if it is worth noting that B. pumilis can be used as a BI to monitor radiation sterilization of drug product components or drug substances that have extremely low bioburden.
Response: Comment not incorporated. The Expert Committee determined that there is no defensible rationale for using a biological indicator with radiation sterilization as the existence of non-spore formers with extreme radiation resistance requires that radiation sterilization be validated based upon the bioburden present as performed for medical devices.
Comment Summary #9: The commenter felt that the text indicates that accurate determination of the lethal conditions for BI's is not possible; however, it also suggests use of BI's. Therefore it should be considered if there should be further explanation, advice, and/or reference for the reader about vapor phase sterilization and validation with BIs.
Response: Comment not incorporated. The Expert Committee determined that there is no inconsistency. The content provided in <1229.11> *Vapor Sterilization* recommends the use of BI's as empirical evidence of vapor sterilization process efficacy. Because the recommendations are for the use of resistant spore formers, confidence in the outcome is assured despite the absence of an accurate D-value.
Comment Summary #9: The commenter suggested including text that indicates the use of screening studies for BI lots in the actual sterilization process is an effective way to gain an understanding of the BI's expected performance under those specific conditions.
Response: Comment not incorporated. The Expert Committee determined that this is outside the scope of this General Chapter.

General Chapter/Sections:	<1229.9> Physicochemical Integrators and Indicators for Sterilization
Expert Committee:	General Chapters—Microbiology
No. of Commenters:	1

Comment Summary #1: The commenter suggested specifying if it this General Chapter is intended to describe the integrators and indicators used in the healthcare setting or by the pharmaceutical industry.
Response: Comment not incorporated. The Expert Committee determined that it deliberately made no distinction with respect to application and thus the General Chapter should be understood as being applicable in all settings.

Comment Summary #2: The commenter suggested including more information on when and how integrators and indicators can be useful and appropriately used to monitor sterilization processes and also when they should not be used.
Response: Comment incorporated. Additional information was added.
Comment Summary #3: The commenter suggested relocating the section on *Indicators* so that it appears before the *Physicochemical Integrators* section.
Response: Comment incorporated.

General Chapter/Sections: <1229.12> New Sterilization Methods
Expert Committee: General Chapters—Microbiology
No. of Commenters: 2
Comment Summary #1: The commenter suggested providing a definition and clarification of the terms used to explain considerations when developing new or novel sterilization processes such as continuous sterilization to align with the concepts presented in the relevant FDA guidance.
Response: Comment not incorporated. The Expert Committee determined that *USP–NF* content on sterilization is intended to be non-specific and not tied to equipment design or application of a sterilization method in a continuous manner, and need not address all possible applications.
Comment Summary #2: The commenter suggested revising text that indicates that when using a new or novel method of sterilization it is the end user's responsibility to demonstrate that the proposed new method can be used safely and effectively for improved clarity.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested switching the first and second bulleted items in the section that discusses the major steps in the implementation of a new sterilization method, because it seems more appropriate that one should determine that no established method will work before embarking upon a literature review of the proposed method.
Response: Comment incorporated

General Chapter/Sections: <2251> Adulteration of Dietary Supplements with Drugs and Drug Analogs/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter indicated that adulterated dietary supplements cannot be considered legitimate dietary supplements under the existing regulatory definition in the Food, Drug and Cosmetic Act (FDCA) and requested that qualifying statements were added to each instance when dietary supplements are mentioned in the General Chapter, or to identify them as “misbranded drugs” throughout the General Chapter.
Response: Comment not incorporated. The Expert Committee will consider appropriate nomenclature in a future revision.
Comment Summary #2: The commenter suggested revising the title of the General Chapter to clarify that the content and the procedures specified therein are not intended for the legitimate dietary supplements. The proposed revised titles were: “*Adulteration of products falsely identified as ‘dietary supplements’ or conventional foods with undeclared misbranded drugs and drug analog*s,” “*Methods for detection of undeclared misbranded drugs and drug analogs in products falsely identified as ‘dietary supplements’ or conventional foods*,” and “*Methods for detection of undeclared misbranded drugs and drug analogs in orally-consumed products*.”

Response: Comment not incorporated. The Expert Committee will consider addressing the title of the General Chapter in a future revision.
Comment Summary #3: The commenter objected to placement of the General Chapter <2251> within the Dietary Supplement Chapters section of *USP–NF*, and suggested it be moved for the reasons discussed in Comment Summaries #1 and #2 above.
Response: Comment not incorporated. Placement of the General Chapter <2251> within the *USP–NF* general chapter hierarchy is consistent with its intent and is informed by its intended use to screen for drugs and drug analogs.

Monograph/Sections: Abacavir and Lamivudine Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 5
Comment summary #1: The commenter recommended adding a second orthogonal identification test.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon the receipt of the necessary supporting data.
Comment summary #2: The commenter indicated that the retention times of abacavir and lamivudine in the briefing are interchanged.
Response: Comment not incorporated. The retention times in the briefing are for information only and are not included in the monograph. The relative retention times in the monograph are correct and reflect the typical retention times of 7 min for lamivudine and 11 min for abacavir.
Comment summary #3: The commenter suggested using an HPLC procedure instead of a UV procedure for analysis of samples in the *Dissolution* test.
Response: Comment not incorporated. The analytical procedure in the Dissolution test is consistent with the approved validated method.
Comment summary #4: The commenter expressed concern about the approach of using multi-component analysis software for evaluating data in the *Dissolution* test.
Response: Comment not incorporated. The Expert Committee determined that the calculation in the *Dissolution* test is consistent with the validated procedure.
Comment summary #5: The commenter indicated that a negative peak at the front of the lamivudine peak in the *Assay* and the test for *Organic Impurities* may cause problems during integration.
Response: Comment not incorporated. The Expert Committee determined that the procedure, which is consistent with the validated method, is suitable for the public standard.
Comment summary #6: The commenter expressed concern about the resolution between carboxylic acid and lamivudine diastereomer in the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee determined that the procedure, which is consistent with the validated method, is adequately selective and is suitable for the public standard.
Comment summary #7: The commenter requested revising the calculation in the test for *Organic Impurities* to quantitate impurities against the Standard solution instead of peak area normalization.
Response: Comment not incorporated. The Expert Committee determined that the procedure is consistent with the validated method.
Comment summary #8: The commenter requested including equilibration time to Table 1 in the *Assay*.
Response: Comment incorporated. A note was added to indicate the re-equilibration time.

Comment summary #9: The commenter requested revising the relative retention time for lamivudine-diastereomer in the *System suitability* section of the *Assay* from 0.95 to 0.88 based on the validation data.
Response: Comment incorporated.
Comment summary #10: The commenter requested using the flexible monograph approach to include their in-house *Organic impurities* procedure.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of the supporting data.

Monograph/Section: Acetazolamide/Organic Impurities
Expert Committee: Chemical Medicines Monographs 3
Expert Committee-initiated Change #1: The Expert committee deferred the test for Organic impurities to further evaluate the proposed procedure based on comments received.

Monograph/Sections: Alprazolam Extended-Release Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter requested adding parentheses in the test for *Organic Impurities* around the value in the acceptance criteria column for named unspecified impurities and to add footnotes indicating that the named impurities are controlled as unspecified impurities under the limit for any individual unspecified impurity.
Response: Comment not incorporated. The Expert Committee may consider changing current *USP-NF* style for this monograph as part of a future revision.

Monograph/Sections: Amiodarone Hydrochloride Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended adding a second *Identification* test.
Response: Comment not incorporated. The Expert Committee will consider future revision to add a second Identification test.
Comment Summary #2: The commenter indicated that the acceptance criteria for the *Assay* are not consistent with the FDA approved specifications.
Response: Comment not incorporated. The acceptance criteria for *Assay* are consistent with FDA requirements.
Comment Summary #3: The commenter suggested revising the acceptance criteria for the individual impurities based on the ICH guidelines and tightening the limits for total impurities and amiodarone related compound D in the test for *Organic Impurities*.
Response: Comment not incorporated. The acceptance criteria for the individual impurities and the total impurities are consistent with FDA requirements.
Comment Summary #4: The commenter recommended tightening the acceptance criteria for Iodide under the test for *Limit for Iodide*.
Response: Comment not incorporated. The acceptance criterion in the *Limit of Iodide* test is consistent with FDA requirements.
Comment Summary #5: The commenter recommended adding a test for osmolality.
Response: Comment not incorporated. The proposed test procedures and acceptance criteria in the monograph reflect FDA requirements.

Monograph/Sections: Argatroban/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the chemical structure of argatroban to indicate the zwitterion nature of the drug substance.
Response: Comment not incorporated. The proposed chemical structure is consistent with the USP naming convention.
Comment Summary #2: The commenter indicated that the acceptance criterion for the total impurities in the test for *Organic Impurities* is not consistent with the FDA approved specifications.
Response: Comment not incorporated. The acceptance criterion for the total impurities is consistent with FDA requirements.
Comment Summary #3: The commenter indicated that the acceptance criteria for (R)-Argatroban and (S)-Argatroban in the test for *Content of Stereoisomers* are not consistent with the FDA approved specifications.
Response: Comment not incorporated. The acceptance criteria for (R)-Argatroban and (S)-Argatroban are consistent with FDA requirements.

Monograph/Sections: Atomoxetine Capsules /Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3
Comment Summary #1: The commenter requested adding parentheses in the test for *Organic Impurities* around the value in the acceptance criteria column of *Table* 1 for Atomoxetine *N*-amide and to add a footnote indicating that this compound is controlled as and unspecified impurity under the limit for any individual unspecified impurity.
Response: Comment not incorporated. The Expert Committee may consider changing current *USP-NF* style for this monograph as part of a future revision.
Comment Summary #2: Commenter requested adding a statement in the test for *Organic Impurities* to indicate that Atomoxetine *N*-amide is not relevant for all manufacturing processes.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data when appropriate.
Comment Summary #3: The commenter requested replacing all of the procedures with their in-house procedures.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Monograph/Sections: Atomoxetine Hydrochloride/ Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3
Comment Summary #1: The commenter requested widening the tailing factor requirement in the test for *Organic Impurities, Procedure 1* from NMT 1.5 to NMT 2.0 for Atomoxetine.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.
Comment Summary #2: The commenter requested widening the acceptance criteria for atomoxetine related compound A and mandelic acid in the test for *Organic Impurities, Procedure 1* from NMT 0.10% each to NMT 0.15% each for consistency with the ICH guideline for known impurities.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data when appropriate.
Comment Summary #3: The commenter requested adding parentheses in the test for *Organic Impurities, Procedure 1* around the values in the acceptance criteria column of Table 1 for mandelic acid and atomoxetine related compound A and to add footnotes indicating that these compounds are controlled as unspecified impurities under the limit for any individual unspecified impurity.
Response: Comment not incorporated. The Expert Committee may consider changing current USP-NF style for this monograph as part of a future revision.

Monograph/Sections: Calcium Pantothenate/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2
Comment Summary # 1: The commenter indicated that the proposed *Assay* lower limit of NLT 98.0% can cause the result out of specifications (OOS) for a lot of manufacturers because of the high uncertainty inherent in the HPLC procedure.
Response: Comment not incorporated. The Expert Committee reviewed the submitted data and found that none of the data failed the required limit. The Expert Committee will consider future revisions to this monograph upon the receipt of the additional supporting data.
Comment Summary #2: The commenter suggested that the proposed *Assay* lower limit be NLT 97.0% to align with that in the FCC Calcium Pantothenate monograph.
Response: Comment not incorporated. The Expert Committee will consider future revision to the lower limit requirement upon the receipt of the additional supporting data.
Comment Summary #3: The commenter recommended that the *European Pharmacopoeia* (EP) titration method be used for the *Assay* as it is more precise and also harmonized with the *EP* monograph.
Response: Comment not incorporated. The Expert Committee considered titration procedure not specific and should not be used for future revisions of the monograph.
Comment Summary #4: The commenter indicated that several impurities (alanyl calcium pantothenate, beta-alanine, and pantolactone) were either not detected or interfered with other peaks when using the proposed HPLC Related Compounds test. They proposed the USP method be replaced with their validated in-house method.
Response: Comment partially incorporated. The Expert Committee requested the proposed *USP Related Compounds* test in the monograph to be put on hold. They also referred the commenter's proposed method to the USP lab for verification. The Expert Committee will consider future revisions to this monograph upon the receipt of data from the USP lab verifying the commenter's method.

Monograph/Section(s): Calcium Succinate/Introduction
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter recommended that the chemical name "Succinic acid calcium salt monohydrate" be replaced with "Calcium Succinate monohydrate."
Response: Comment incorporated**.**

Monograph/Sections: Candesartan Cilexetil Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the acceptance criterion for total impurity from NMT 4.0% to NMT 3.0% to be consistent with FDA requirements.
Response: Comment incorporated.

Monograph/Sections: Carbidopa and Levodopa Extended-Release Tablets/Multiple sections
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated Change #1: An analysis section was added to *Dissolution Test* 3 for consistency with the sponsor's submission and with the *USP–NF* style for this monograph.
Expert Committee-initiated Change #2: The phrase "into the chromatograph" was removed from the statement at the beginning of the test for *Organic Impurities*.
Expert Committee-initiated Change #3: In *Table* 1 within the test for *Organic Impurities*, a footnote reference was added to indicate that levodopa related compound B is monitored in the drug substance is not to be reported nor included in the Total degradants.
Expert Committee-initiated Change #4: The chemical name for USP Levodopa Related Compound B RS was updated for consistency with the Reference Standard label and other *USP–NF* monographs.

Monograph/Sections: Carbidopa and Levodopa Orally Disintegrating Tablets/ Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated Change #1: The phrase "into the chromatograph" was removed from the statement at the beginning of the test for *Organic Impurities*.
Expert Committee-initiated Change #2: In *Table* 1 within the test for *Organic Impurities*, carbidopa related compound A was renamed 3-*O*-methyl carbidopa for consistency with other *USP–NF* monographs and a corresponding footnote was added to provide its chemical name.

Monograph/Sections: Cetylpyridinium Chloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1
Comment Summary #1: The commenter stated that there should be a correction factor applied to the concentration of reference standard solution based on their purity.
Response: Comment not incorporated. Purity of USP reference standard is listed in the RS label or certificate.
Comment Summary #2: The commenter requested the word chloride be added after cetylpyridinium in the *Assay* and *Organic Impurities* sections.
Response: Comment not incorporated. The Expert Committee determined the statement is consistent with the chemical form of the impurity peak.
Comment Summary #3: The commenter stated that the definition to one of the variables in the equation under Organic Impurities, "r_S = peak response of cetylpyridinium from the Standard solution," should have the word chloride added after cetylpyridinium.
Response: Comment not incorporated. The Expert Committee determined that the description of peak response $r_{S,}$ correctly depicts the chemical form of the impurity peak.

Comment Summary #4: The commenter requested not to widen the *Assay* acceptance criteria from NLT 99.0% to NLT 98.0% due to the potential impact on the impurities and product quality.
Response: Comment not incorporated. The Expert Committee determined that the proposed acceptance criteria in *Assay* and *Organic Impurities* sections can adequately establish the product quality.

Monograph/Sections: Cyanocobalamin Tablets/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter commented that the following phrase in the labeling section: "The Label also states whether it is to be disintegrated in the mouth" is not clear enough for the intention.
Response: Comment incorporated. The statement was rephrased as "Tablets that are intended to be disintegrated in the mouth before swallowing are so labeled."
Comment Summary #2: The commenter commented that the term 'disintegrated' is not easily understandable by lay people and therefore is not friendly to a dietary supplement label.
Response: Comment not incorporated. The Expert Committee determined that the term was appropriate.

Monograph/Sections: Diltiazem Hydrochloride Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the acceptance criteria for desacetyl diltiazem from NMT 0.5% to NMT1.5% and the total impurities from NMT1.0% to NMT 2.0% to be consistent with FDA requirements.
Response: Comment incorporated.

Monograph/Sections: Diphenhydramine Hydrochloride and Ibuprofen Capsules/ Organic Impurities
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1
Comment Summary #1: The commenter requested including specifications for ibuprofen related impurities.
Response: Comment not incorporated. The specifications are consistent with FDA requirements. The Expert Committee will consider future revisions upon receipt of the supporting data.

Monograph/Sections: Dronedarone Hydrochloride/Organic Impurities
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2
Comment Summary #1: The commenter indicated that the typical retention time for dronedarone under the Organic Impurities test is about 37 min and not about 34 min.
Response: Comment not incorporated. The retention time for dronedarone is included in the Briefing section for informational purposes.
Comment Summary #2: The commenter indicated that some of the impurities have broad peak shapes under the test for Organic Impurities.

Response: Comment not incorporated. The Expert Committee determined that the procedure is suitable as written.
Comment Summary #3: The commenter indicated that the Organic Impurities procedure is not specific for their process related impurities which are not specified in the test for Organic Impurities.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.
Comment Summary #4: The commenter requested including their process specific impurities and the corresponding acceptance criteria under the test for Organic Impurities.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Monograph/Sections: Dronedarone Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 3
Comment Summary #1: The commenter recommended adding column equilibration time of 6 h in the test for *Assay* as it affects the resolution.
Response: Comment not incorporated. The Expert Committee determined the proposed procedure is suitable as written and will consider future revisions if needed.
Comment Summary #2: The commenter indicated that an unknown peak at relative retention time of 0.76 is co-eluting with dronedarone related compound A peak.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.
Comment Summary #3: The commenter indicated that two unknown peaks are closely eluting as shoulder to the dronedarone peak.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.
Comment Summary #4: The commenter indicated that their product has different dissolution medium and tolerances.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.
Comment Summary #5: The commenter requested revising *Assay* acceptance criteria from 90.0%–110.0% to 90.0%–105.0%.
Response: Comment not incorporated. The *Assay* acceptance criteria are consistent with FDA requirements.
Comment Summary #6: The commenter requested revising the relative retention time for dronedarone related compound A from 0.8 to 1.43.
Response: Comment not incorporated. The relative retention time is consistent with the validated procedure.
Comment Summary #7: The commenter requested correcting the calculations by revising Mr1 and Mr2 in the test for the *Assay*, *Dissolution* and *Organic Impurities* sections to be consistent with the label claim.
Response: Comment incorporated.
Comment Summary #8: The commenter indicated that the resolution criterion for impurities is very stringent.

Response: Comment not incorporated. The Expert Committee determined that the resolution requirement in the monograph is suitable as proposed and will consider future revisions if needed.
Comment Summary #9: The commenter indicated that the tolerances under the *Dissolution* test are not consistent with FDA requirements.
Response: Comment not incorporated. The proposed tolerances are consistent with FDA requirements.

Monograph/Sections: Duloxetine Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2
Comment Summary #1: The commenter requested adding parentheses in the test for *Organic Impurities* around the values in the acceptance criteria column of *Table* 1 for duloxetine alcohol, duloxetine 4-napthyl isomer, alpha-naphthol, and duloxetine beta-naphthol-1-yl isomer and to add footnotes indicating that these compounds are controlled as unspecified impurities under the limit for any individual unspecified impurity.
Response: Comment not incorporated. The Expert Committee may consider changing the current *USP-NF* style of the monograph as part of a future revision.
Comment Summary #2: The commenter requested replacing the existing test for the *Limit of Duloxetine Related Compound A* with their in-house procedure which has a shorter run time.
Response: Comment not incorporated. This comment is outside the scope of the current revision proposal. The Expert Committee will consider this comment as a request for a future revision.
Comment Summary #3: The commenter requested replacing the existing test for *Organic Impurities* with their in-house procedure because the existing test is not specific for duloxetine related compound A.
Response: Comment not incorporated. This comment is outside the scope of the current revision proposal. The Expert Committee will consider this comment as a request for a future revision.

Monograph/Sections: Fluorometholone/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter noted that the “total Impurities” acceptance criterion is not consistent with FDA criterion.
Response: Comment not incorporated. The limit for “total Impurities” is consistent with FDA requirements.
Comment Summary #2: The commenter requested the chemical name for fluorometholone related compound A be added in *Table* 1.
Response: Comment not incorporated. The *USP-NF* current monograph style is not to include the chemical name of reference standards in Tables. Chemical information for the related compound is found in the *USP Reference Standards* <11> section of the monograph.

Monograph/Section(s): Ginger/Identification Test C
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
Expert Committee-initiated Change #1: The concentration and the application volume of the Standard Solution A were modified to better accommodate handling of the USP Ginger Constituent Mixture RS.
Expert Committee-initiated Change #2: Glacial acetic acid was explicitly specified in preparation of the Derivatization reagent.
Expert Committee-initiated Change #3: Latin binomials were included to properly identify potential adulterants and confounders: Katsumada's galangal (*Alpinia hainanensis* K.Schum.), sharpleaf galangal (*Alpinia oxyphylla* Miq.) kaempferia galanga (*Kaempferia galanga* L.) and lesser galangal (*Alpinia officinarum* Hance).

Monograph/Section(s): Powdered Ginger/Identification Test C
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
Expert Committee-initiated Change #1: The concentration and the application volume of the Standard Solution A were modified to better accommodate handling of the USP Ginger Constituent Mixture RS.
Expert Committee-initiated Change #2: Glacial acetic acid was explicitly specified in preparation of the Derivatization reagent.
Expert Committee-initiated Change #3: Latin binomials were included to properly identify potential adulterants and confounders: Katsumada's galangal (*Alpinia hainanensis* K.Schum.), sharpleaf galangal (*Alpinia oxyphylla* Miq.) kaempferia galanga (*Kaempferia galanga* L.) and lesser galangal (*Alpinia officinarum* Hance).

Monograph/Section(s): Ginger Tincture/ Identification Test C
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
Expert Committee-initiated Change #1: The concentration and the application volume of the Standard Solution A were modified to better accommodate handling of the USP Ginger Constituent Mixture RS.
Expert Committee-initiated Change #2: Glacial acetic acid was explicitly specified in preparation of the Derivatization reagent.
Expert Committee-initiated Change #3: Latin binomials were included to properly identify potential adulterants and confounders: Katsumada's galangal (*Alpinia hainanensis* K.Schum.), sharpleaf galangal (*Alpinia oxyphylla* Miq.) kaempferia galanga (*Kaempferia galanga* L.) and lesser galangal (*Alpinia officinarum* Hance).

Monograph/Sections: Goldenseal/Composition
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
Expert Committee-initiated Change #1: Palmatine chloride was specified in place of palmatine in preparation of the System suitability solution.

Monograph/Sections: Powdered Goldenseal/Composition
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
Expert Committee-initiated Change #1: Palmatine chloride was specified in place of palmatine in preparation of the System suitability solution.

Monograph/Sections: Powdered Goldenseal Extract
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
Expert Committee-initiated Change #1: Palmatine chloride was specified in place of palmatine in preparation of the System suitability solution.

Monograph/Section: Glyburide and Metformin Hydrochloride Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter requested including their approved parameters and tolerances as *Dissolution Test* 2.
Response: Comment incorporated. A labeling section was added to support the inclusion of *Dissolution Test* 2.
Expert Committee-initiated Change #1: The statement in *Identification* test A for *Glyburide* was modified to be consistent with the statement in *Identification* test B for *Metformin Hydrochloride.*

Monograph/Sections: Hydromorphone Hydrochloride/Assay
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Expert Committee-initiated Change #1: The revisions proposed under *Assay* were cancelled based on the data indicating the split peak from the Standard solution
Expert Committee-initiated Change #2: Because the changes proposed in *Assay* were cancelled, the associated changes in the *Definition* were also cancelled.
Expert Committee-initiated Change #3: Because the changes proposed in *Assay* were cancelled, the addition of *Identification* B was also cancelled.
Expert Committee-initiated Change #4: Because the changes proposed in *Assay* were cancelled, the editorial changes (format changes) proposed in *Organic impurities*, *Procedure* 2 were also cancelled.

Monograph/Section(s): Isoleucine
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter indicated that they observed three unspecified peaks (1.5, 1.7, and 7.8 min) in *Blank*, *Standard* and *Sample solutions*. They were not sure whether they should consider them as unspecified impurities or not, and requested USP to include a statement in the procedure to indicate that these peaks should not be considered as unspecified impurities.
Response: Comment not incorporated. The USP validation data confirmed that the peaks at 1.5 and 1.7 min are solvent peaks. The data did not confirm the peak at 7.8 min. The Expert Committee believes that the request for adding a statement in the procedure is unnecessary, because a well-trained analyst should be able to determine whether a peak is an impurity or solvent/artifactual peak by comparing the chromatograms from the blank and sample solutions.
Comment Summary #2: The commenter proposed that the amino acid analyzer method for characterizing the related compounds be incorporated into the revision of the monograph because it is more precise.

Response: Comment not incorporated. The Expert Committee may consider the application of amino acid analyzer method for future revisions to the USP amino acid monographs, not as a replacement of the current method, but as an alternative or complementary method.

Monograph/Section(s): Krill Oil
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2
Comment Summary #1: The commenter proposed that the upper limit of total phospholipids be increased from NMT 55% to NMT 59% due to new data recently obtained.
Response: Comment incorporated.
Comment Summary #2: The commenter proposed several changes to the fatty acid profile in the *Identification* test. The proposed changes involve the removal of alpha-linolenic acid and moroctic acid, and changes to the range limits for eicosenic acid, erucic acid, and linoleic acid. The commenter proposed the changes to reflect the relatively large variability of these fatty acids based on the source (krill catch) season-to-season and year-to-year basis.
Response: Comment incorporated.
Comment Summary #3: The commenter proposed that the sentence "Phosphatidylcholine: 60%-96% (w/w) of the *total phospholipids content*" be changed to, "Phosphatidylcholine (sum of PC + 1-LPC + 2-LPC): 60%-96% (w/w) of the *total phospholipids content*" for clarification purpose.
Response: Comment incorporated.
Comment Summary #4: The commenter proposed that the tests for *Acid value* and *Unsaponifiable Matter* be removed from the monograph because they have no added value to the characterization of krill oil.
Response: Comment incorporated.

Monograph/Section(s): Leucine
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter indicated that they observed three unspecified peaks (1.5, 1.7, and 7.8 min) in *Blank*, *Standard* and *Sample solutions*. They were not sure whether they should consider them as unspecified impurities or not, and requested USP to include a statement in the procedure to indicate that these peaks should not be considered as unspecified impurities.
Response: Comment not incorporated. The USP validation data confirmed that the peaks at 1.5 and 1.7 min are solvent peaks. The data did not confirm the peak at 7.8 min. The Expert Committee believes that the request for adding a statement in the procedure is unnecessary because a well-trained analyst should be able to determine whether a peak is an impurity or solvent/artifactual peak by comparing the chromatograms from the blank and sample solutions.
Comment Summary #2: The commenter indicated that the proposed *Related Compounds* test could not separate the leucine impurity peak completely from isoleucine main peak and therefore, it was difficult to quantify leucine accurately. They requested the proposed method be modified.
Response: Comment not incorporated. The USP validation data confirmed that the impurity leucine is well separated from the isoleucine main peak.

Comment Summary #3: The commenter proposed that the amino acid analyzer method for characterizing the related compounds be incorporated into the revision of the monograph because it is more precise.
Response: Comment not incorporated. The Expert Committee may consider the application of amino acid analyzer method for future revisions to the USP amino acid monographs, not as a replacement of the current method, but as an alternative or complementary method.

Monograph/Sections: Levothyroxine Sodium/Identification
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the concentration of sulfuric acid solution in *Identification* test C from 1 N to 2 N to harmonize with the *European Pharmacopoeia* monograph.
Response: Comment incorporated.
Expert Committee-initiated Change #1: A note is added to allow the use of an alternative procedure for ignition under *Identification* test C.

Monograph/Sections: Lufenuron/Multiple Sections
Expert Committees: Chemical Medicines Monographs 3
No. of Commenters: 2
Comment Summary #1: The commenter requested listing lufenuron related compound G as an unspecified impurity to be consistent with FDA requirements.
Response: Comment incorporated. Lufenuron related compound G was removed from Table 1 in the test for *Organic impurities* and the relevant relative retention time information was added to the system suitability section.
Expert Committee-initiated Change #1: The chemical name for lufenuron related compound C in the *USP Reference Standards <11>* section was revised to correct an unpaired bracket.

Monograph/Sections: Orphenadarine Citrate/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter requested the limit of Orphenadrine Related Compound C, a metabolite, be widened from NMT 0.2% to NMT 0.3% to be consistent with their approved limit
Response: Comment incorporated
Comment Summary #2: The commenter requested the inclusion of diphenhydramine with the appropriate relative retention time and a limit of NMT 0.3%
Response: Comment incorporated

Monograph/Section: Palonosetron Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 2
Comment Summary #1: The commenter requested revising the limit of palonosetron enantiomer from NMT 0.1% to NMT 0.15% in the test for *Limit of Specified Impurities*.
Response: Comment not incorporated. The acceptance criteria in the proposal are consistent with FDA requirements.

Comment Summary #2: The commenter requested adding another specified impurity, *N*-[(3*S*)-quinuclidin-3-yl]-5,6,7,8-tetrahydronaphthalene-1-carboxamide, to the Table 1 in the test for *Limit of Specified Impurities***.**
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon the receipt of supporting data.
Expert Committee-initiated change #1: The *USP Reference Standards <11>* section was revised to change the trivial name of palonosetron related compound C from "palonosetron diastereomer" to "palonosetron *S,R*-diastereomer" and to include a second trivial name "palonosetron *R,S*-diastereomer" for palonosetron related compound D.

Monograph/Sections: Perindopril Erbumine/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 4
Comment Summary #1: The commenter requested widening the *Assay* acceptance criteria from 99.0%-101.0% to 98.0%-102.0% to be consistent with FDA requirements.
Response: Comment incorporated.
Comment Summary #2: The commenter requested adding two impurities in the test for *Organic Impurities*, perindopril related compound E, and perindopril related compound H along with the corresponding acceptance criteria of NMT 0.40% and NMT 0.15% respectively.
Response: Comment incorporated.
Comment Summary #3: The commenter requested adding the acceptance criterion of 3.00%-4.50% for the monohydrate form in the test for *Water Determination*, for a hydrated form of perindopril erbumine, to be consistent with FDA requirements.
Response: Comment incorporated.
Comment Summary #4: The commenter requested including an identification test for counter ion tert-butyl amine
Response: Comment not incorporated. The Expert Committee determined that the current identification test procedures adequately establish the identity of the drug substance.
Comment Summary #5: The commenter indicated that the Sample solution concentration under the *Assay* is too low to achieve a precision for 99.0%-101.0%.
Response: Comment not incorporated. The *Assay* acceptance criteria are revised from 99.0%–101.0% to 98.0% –102.0%.
Comment Summary #6: The commenter requested deleting the third chemical name for perindopril erbumine, as it corresponds to epi-perindopril.
Response: Comment incorporated.
Comment Summary #7: The commenter requested including the chemical name for perindopril related compound I under the test for *Limit of perindopril related compound* I.
Response: Comment incorporated.
Comment Summary #8: The commenter indicated that it is difficult to consistently meet the tailing factor requirement for *Assay*.
Response: Comment not incorporated. The Expert Committee determined that the suitability requirement for tailing factor in *Assay* is suitable as proposed.
Comment Summary #9: The commenter requested not including the USP Perindopril Related Compound B RS, USP Perindopril Related Compound C RS, USP Perindopril Related Compound D RS, and USP Perindopril Related Compound F RS in the System suitability solution for identification purposes.

Response: Comment not incorporated. The Expert Committee determined that it is useful to include the reference materials when available for identification purposes in a monograph.

Monograph/Sections: Perindopril Erbumine Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 3
Comment Summary #1: The commenter requested widening the acceptance criteria for the perindopril related compound F from NMT 2.0% to NMT 3.0% to be consistent with FDA requirements.
Response: Comment incorporated.
Comment Summary #2: The commenter requested widening the acceptance criteria for the total impurities from NMT 1.5% to NMT 3.0% to be consistent with the FDA approved product specifications.
Response: Comment not incorporated. The Expert Committee determined that the proposed specification for total impurities not including perindopril related compound B and perindopril related compound F will accommodate all FDA approved products.
Comment Summary #3: The commenter questioned whether it is necessary to include perindopril related compound C, perindopril related compound D, or perindopril related compound I as specified impurities.
Response: Comment not incorporated. The Expert Committee determined that the proposed specifications are adequate for a public standard intended to address all FDA approved products.
Comment Summary #4: The commenter recommended using the procedures from the *British Pharmacopoeia* for the *Assay*, *Impurities*, and *Dissolution* sections.
Response: Comment not incorporated. The Expert Committee determined that the proposed procedures in monograph are suitable for the intended purpose.
Comment Summary #5: The commenter requested deleting the test for perindopril related compound I as it is a process related impurity.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended revising the UV diode array based procedure for Identification test A to an Infra-Red spectroscopy based test procedure.
Response: Comment not incorporated. The Expert Committee will consider future revision upon receipt of supporting data.

Monograph/Section: Rabeprazole Sodium/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 3
Comment Summary #1: The commenter requested using a diluted test solution for quantitation of impurities in the test for *Organic impurities*.
Response: Comment not incorporated. The USP approach is to employ a Standard solution using the relevant USP Reference Standard for quantitation of impurities.
Comment Summary #2: The commenter recommended deleting the resolution requirement between rabeprazole related compounds D and F in the test for *Organic impurities*, to make the system suitability requirements consistent with *European Pharmacopoeia* monograph.
Response: Comment incorporated.

Comment Summary #3: The commenter requested including the hydrated form in the chemical information section of the monograph, and updating the label of USP Rabeprazole Sodium RS to indicate whether it is anhydrous or a hydrate.
Response: Comment incorporated. The USP Rabeprazole Sodium RS label was updated to indicate the hydrated form.
Comment Summary #4: The commenter stated that it is not necessary to protect rabeprazole sodium solution from light, and requested removing the *Note* under the *Assay* and *Organic impurities* tests.
Response: Comment not incorporated. The statement requiring protection of rabeprazole sodium solutions from light is consistent with the validated procedure.
Comment Summary #5: The commenter indicated that they manufacture an amorphous form of material with the limit of water of NMT 7.0%, and requested to include the amorphous form in the monograph.
Response: Comment not incorporated. Both anhydrous and hydrated forms of rabeprazole sodium could be amorphous. Because the commenter's material has a water limit of NMT 7.0%, it is a hydrated form.

Monograph/Section(s): *Rhodiola rosea* Capsules/Definition
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary: The commenter proposed that the Expert Committee add chemical formulas for rosin, rosarin, and rosavin to the *Definition* section.
Response: Comment incorporated.

Monograph/Section(s): *Rhodiola rosea* Tablets/Definition
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary: The commenter proposed that the Expert Committee add chemical formulas for rosin, rosarin, and rosavin to the *Definition* section.
Response: Comment incorporated.

Monograph/Sections: Sildenafil Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 2
Comment Summary #1: The commenter requested revising the acceptance criteria for "Total Impurities" in the test for *Organic Impurities* to be consistent with FDA requirements.
Response: Comment not incorporated. The limit for Total Impurities is consistent with FDA requirements.
Comment Summary #2: The commenter requested that the monograph title be revised from "Sildenafil Tablets" to Sildenafil Citrate Tablets."
Response: Comment not incorporated. The Expert Committee determined that the monograph title is appropriate for this drug product.
Comment Summary #3: The commenter requested revising the acceptance criteria for "any individual unspecified degradation product" in the test for *Organic Impurities* from NMT 0.20% to NMT 0.2% to match ICH expectations.
Response: Comment not incorporated. The limit for "any individual unspecified degradation product" is consistent with FDA requirements.

Monograph/Section: Sodium Starch Glycolate/Identification A
Expert Committees: Excipient Monograph 2
No. of Commenters: 1
Comment Summary #1: The commenter indicated that they have not observed the infrared absorption peaks contributed by citrate in the Sodium Starch Glycolate reference standard and believe that citrate should be considered an impurity in the Sodium Starch Glycolate. They recommended including a test and a limit to ensure that citrate remains below an acceptable level and Sodium Starch Glycolate remains a pure material.
Response: Comment not incorporated. The intent of the statement for disregarding those peaks attributed to the presence of citrate is to provide an allowance for materials that may or may not contain citrate in the neutralization step of the manufacturing process when compared to a reference material that uses a different neutralization agent. The recommendation to include a test and limit for citrate will be considered by the Expert Committee in future revisions to this monograph upon the receipt of supporting data.

Monograph/Sections: Sulindac/ Multiple Sections
Expert Committees: Chemical Medicines Monographs 2
No. of Commenters: 2
Comment Summary #1: The commenter recommended rounding the percent of relative standard deviation under *Assay* from NMT 0.73% to NMT 1.0 %.
Response: Comment not incorporated. The validation data supports the proposed acceptance criteria for the percent of relative standard deviation.
Comment Summary #2: The commenter requested revising the UHPLC procedure for the *Assay* and/or *Organic impurities*, because there is no UHPLC technology in house and this may not be suitable for a public standard.
Response: Comment not incorporated. The Expert Committee determined that UHPLC is suitable for the intended use and will consider a future revision to the monograph.
Expert Committee-initiated Change #1: The Expert Committee revised the chemical formula for sulindac related compound B from $C_{17}H_{17}FO_4S$ to $C_{20}H_{17}FO_4S$ to be consistent with the reported impurity in the drug product.

Monograph/Section(s): Sulindac Tablets/ <11> USP Reference Standards
Expert Committee(s): Chemical Medicines Monographs 2
No. of Commenters: 1
Expert Committee-initiated Change #1: The Expert Committee revised the chemical formula for sulindac related compound B from $C_{17}H_{17}FO_4S$ to $C_{20}H_{17}FO_4S$ to be consistent with the reported impurity in the drug product.

Monograph/Section: Teniposide/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the impurity profile in *Table* 2 in the test for *Organic impurities* is different from FDA requirements.
Response: Comment not incorporated. The Expert Committee determined that the impurity profile in the test for *Organic impurities* is appropriate for a public standard.

Expert Committee-initiated Change #1: The word “potentially” was deleted from the *Caution statement* under the *Definition*, because teniposide is proven to be a cytotoxic agent.

Monograph/Section: Teniposide Injection/Definition
Expert Committee: Chemical Medicines Monographs 3
Expert Committee-initiated Change #1: A *Caution* statement, “Great care should be taken in handling teniposide, because it is a cytotoxic agent” was added under *Definition*.

Monograph/Section: Triamcinolone Acetonide Nasal Spray/Multiple
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2
Comment Summary #1: The commenter requested the inclusion of an orthogonal identification procedure
Response: Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
Comment Summary #2: The commenter indicated that impurity profile is different from FDA requirements.
Response: Comment not incorporated. The limits are consistent with FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
Comment Summary #3: The commenter indicated that the limit of triamcinolone acetonide related compound A is different from FDA requirements.
Response: Comment not incorporated. The limits are consistent with FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
Comment Summary #4: The commenter indicated that the acceptance criteria for *Delivered Dose Uniformity* are different from FDA requirements. **Response:** Comment not incorporated. The limits are consistent with FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
Comment Summary #5: The commenter indicated that the acceptance criteria for *Microbial Enumeration Tests* are different from FDA requirements.
Response: Comment not incorporated. The limits are consistent with FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
Comment Summary #6: The commenter requested that the concentration of benzalkonium chloride be lowered from 0.4 mg/mL to 0.05 mg/mL to minimize the peak shape distortion.
Response: Comment incorporated.

Monograph/Section(s): Ubiquinol/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter requested that the chemical structure and the chemical name of ubiquinol be corrected.
Response: Comment incorporated.
Comment Summary #2: The commenter requested that the test for *Water Determination*, *Method 1a* be changed to *Method 1c* because the *Method 1a* did not work consistently.
Response: Comment incorporated.

Monograph/Sections: Vardenafil Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 2
Comment Summary #1: The commenter recommended the addition of a solubility test.
Response: Comment not incorporated. Solubility tests are not compendial requirements and are not included in *USP–NF* monographs, but description and solubility information for Vardenafil Hydrochloride is included in the *Description & Solubility* section of the *USP-NF.*
Comment Summary #2: The commenter requested revising the storage conditions under *Packaging and storage* to indicate a numerical temperature range or stating "Store at controlled room temperature."
Response: Comment not incorporated. The Expert Committee determined that the stability data supports the storage conditions provided in the monograph.
Comment Summary #3: The commenter requested the removal of the system suitability solution in the *Assay*, which is used for resolution, because it is also used for resolution in the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee determined that the test procedure is consistent with the validation data and suitable for its intended use.
Comment Summary #4: The commenter requested that impurities be calculated against a diluted Sample solution instead of a dilute Standard solution in the test for *Organic Impurities* to harmonize with the method of calculation in the corresponding monograph for Vardenafil Hydrochloride in the *European Pharmacopoeia*.
Response: Comment not incorporated. The Expert Committee determined that the method of calculation is consistent with the validation data and suitable for its intended use.

Monograph/Section: Warfarin Sodium/Organic Impurities
Expert Committee: Chemical Medicines Monographs 3
Expert Committee-initiated Change #1: The *run time* in the test for *Organic impurities* is revised from "20 min" to "NLT 2 times the retention time of warfarin peak" for consistency with current USP format.
Expert Committee-initiated Change #2: "Alice's ketone" in *Table* 1 is revised to "Alice's ketone (sodium salt of warfarin related compound A)" for clarity. The footnote for Alice's ketone in *Table 1* is also revised to include "It is sodium salt of warfarin related compound A" followed by the chemical name.

Monograph/Section: Zolmitriptan/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3
Comment Summary #1: The commenter requested the widening of the water limit from NMT 0.5% to NMT 1.0% to be consistent with their approved limit.
Response: Comment incorporated.
Comment Summary #2: The commenter indicated that the *Assay* acceptance criteria are different from FDA requirements.
Response: Comment not incorporated. The limits are consistent with FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
Comment Summary #3: The commenter indicated that the drug substance may contain a potential genotoxic impurity and therefore requested the inclusion of a procedure to monitor that genotoxic impurity.

Response: Comment not incorporated because there is no evidence indicating the presence of a potentially genotoxic impurity. The Expert Committee will consider revising the monograph upon receipt of supporting data.
Comment Summary #4: The commenter indicated that zolmitriptan related compound A co-elutes with desmethyl zolmitriptan
Response: Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
Comment Summary #5: The commenter indicated that use of capillary electrophoresis for limit of zolmitriptan R-isomer is cumbersome.
Response: Comment not incorporated. The Expert Committee has determined that the procedure is suitable for the intended purpose.

Monograph/Section: Zolmitriptan Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3
Comment Summary #1: The commenter requested the inclusion of the use of deaerated medium for dissolution test to be consistent with their approved application.
Response: Comment incorporated.
Comment Summary #2: The commenter requested the widening of the limit of zolmitriptan related compound E from NMT 0.5% to NMT 0.6% to be consistent with FDA requirements.
Response: Comment incorporated.
Comment Summary #3: Two commenters indicated that total degradation products limit should be widened from NMT 0.7% to NMT 1.5% to be consistent with FDA requirements.
Response: Comment incorporated.